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PRACTICE OF ALLERGY

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BY

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Richmond, Virginia

Revised by

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Dallas, Texas

Second Edition



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TO
MY FORMER CHIEF
HENRY ASBURY CHRISTIAN

Quod aliis cibus est aliis fuit acre venenum

—Lucretius

De Rerum Natura, IV, 637.

PREFACE TO SECOND EDITION

The first edition of the *Practice of Allergy* appeared in 1939, and immediately received a warm and widespread reception by those interested in the comparatively new field of allergy, and became an important addition to their bookshelves and a reference source which was appealed to often.

The progress made in this phase of medical practice with the accumulation of new facts, new data, and new theories made a second edition desirable within a few years, and Doctor Vaughan was collecting the material for this edition at the time of his death. Necessarily, work was interrupted and delay in the appearance of this edition was inevitable.

We have realized, as all men must, that it is a very difficult thing to "fill another man's shoes," particularly when the owner of the shoes happened to be a man of exceptional size. Warren Vaughan was no common person, and it has required no common effort to equal his quality as we have made additions to the book.

We have, in every instance, tried to retain the quality and the flavor of the book so that it might remain as it was written, "Warren Vaughan's book." It was the quality and the flavor which he gave it that made for its great popularity, and we hope it remains as distinctive as it was when he wrote it. We have added new material which has appeared, and removed any which, by the passing of years and accumulation of knowledge, has been made unacceptable. Where there is room for honest difference of opinion and his opinion differed from ours, we have retained his. Where advancement in our knowledge has made an opinion no longer tenable, we have not hesitated to change it as he would have changed it if he had lived to see this day.

We are greatly indebted to Mr. O. C. Durham, Chief Botanist of the Abbott Laboratories, Chicago, and Technical Director of the Committee on National Pollen Survey, for the chapters on Field Surveys and Aerobiology: Development and Technique. His authorship of these chapters makes them authoritative.

Dr. J. B. Howell, Dallas, has rewritten the chapter on Fungus Infection With Associated Allergy, so that it represents the present thinking of the dermatologist and the allergist. This new material, we believe, will prove very helpful.

The chapter on Vital Capacity has been rewritten by Dr. James Holman, Dallas, who has recently been engaged in research on problems in this field. The new material in this chapter is an excellent résumé of the present knowledge.

If those to whom this volume comes may find it worthy of the same generous reception which it received in its first edition, we shall be pleased.

HARVEY BLACK.

PREFACE TO FIRST EDITION

In 1930, when "Allergy and Applied Immunology" was written, clinical allergy was very much in its infancy, having passed little more than its first decade of existence. The literature of the subject, while reasonably abundant, was meager as compared with that which has accumulated since, and it was possible to formulate a monograph which would be equally valuable to the physician and to the patient. This was still true, although in lessening degree, in 1934, when the second edition appeared. When the time arrived for a third, it was realized that a combined manual for doctor and patient was no longer logical. The wealth of accumulated information, as well as its technicalities, required separation of the material into two categories. This volume is, therefore, written entirely for the physician and other serious students of the subject. Not only does the separation facilitate the presentation of the subject as a complete technical treatise, but it has simplified the presentation to the patient, as is being done in the small companion volume, "Primer of Allergy."

The student of allergy must interest himself in many fields other than medicine. He must become reasonably conversant with botany, must become a fair mycologist, must be well versed in dietetics, and should be an accurate bacteriologist. He will be a better allergist if he is at the same time a good dermatologist, gastroenterologist, pediatricist, and otolaryngologist. While this is well nigh impossible, fortunately the ideal can be approximated, and indeed improved upon, by collaboration with others expert in these fields. Certain sections, such as those concerning the history of foods and the general mycologic discussion, are included in order that the reader may broaden his general knowledge of the subject.

The methods of testing and treatment described are those which I have found efficacious in my own work, and are not necessarily those preferred by other allergists. For completeness, those recommended by others have been incorporated, with due credit.

Except for the few otherwise credited, all photographs are my own, made with a Leica camera and its attachments for precision work. This includes the photomicrographs of pollens, fungi, lung tissue, ligule enlargements, reproductions of roentgenograms and the clinical and botanical illustrations.

Special acknowledgment is due Dr. Frederick W. Shaw for the chapter and illustrations on identification of fungi; Mr. William B. Brierly who, with the late Dr. Earl B. McKinley, has prepared a volume on the Cartography of Disease, for the dot maps and isopoll map of the United States; Mr. John P. Tillery whose instruction in technical photography and chart-making has been of inestimable value and who prepared the migraine charts; my niece, Mrs. Elizabeth V. Potter, who made the line drawings of genetically related foods and the general fungus drawings; Mr. J. Smith Knapp for the gift of a number of pollen specimens for photomicrography; the late Dr. T. Wingate Todd who edited and approved the section on the growth of the allergic child; Mr. O. C. Durham, who prepared Table XXXIX; Drs. W. Randolph Graham and David M. Pipes who, in taking over much of the office routine, have made the writing

possible; those other physicians of the Clinic who have contributed investigative work and the section on the preparation of test extracts, Drs. Clement J. Sullivan, Glenn D. Grubb, J. Warriek Thomas (who has made many of the charts), and Kenneth L. McLarand; my secretary, Miss Helen Hooper; and The C. V. Mosby Company, who have not hesitated to undertake publication of this volume.

Without the patient understanding and aid of my wife in the polishing of the manuscript, the correction of proof, and the making of illustrations, I would have found my task much less pleasant and less congenial.

W. T. V.

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PART I

STEPS IN THE DEVELOPMENT OF OUR PRESENT UNDERSTANDING OF CLINICAL ALLERGY

Une substance insuffisante à tuer ou même à rendre malade un animal normal, détermine des accidents foudroyants et mortels chez un animal qui, longtemps auparavant, avait reçue cette même substance.

—RICHET

CHAPTER I

INTRODUCTORY

To Jean Alfred Fournier, the great syphilographer of the nineteenth century, is accredited the expression, "To know syphilis is to know medicine." This was indeed true in the days in which the multitudinous manifestations of syphilitic infection, not yet clearly understood, justified the designation of syphilis as *the great imitator*.

Allergy and internal medicine. Today we might paraphrase the famous dictum of Fournier, with slightly different intention, in saying, "To know allergy one must know medicine." Allergy is a constitutional or systemic phenomenon, predominantly functional, only secondarily organic, which may occur in any individual suffering from any other specific malady and which not infrequently colors the picture of the latter disease. The student of allergy must be a student of medicine, well versed in the symptoms of those diseases, infectious, metabolic or degenerative, to which man is heir, and thoroughly conversant with the appropriate therapeutic measures for each.

It is true that allergic manifestations in and of themselves partake of a clear-cut pattern that usually allows ready recognition, and often appear entirely independently of any other disease symptom. In such instances the picture is obvious and indicates the need for clearly defined therapeutic procedures. Even so, however, the treatment should be adjusted to the individual as an individual rather than to the symptom as a specific disease manifestation. Thus, although the most effective immediate therapy of acute asthma is in the form of adrenalin injections, this should be given with great caution to an asthmatic with severe hypertension.

Indeed, there is little or no place in the practice of medicine for the so-called specialist in allergy, or, worse, the "specialist in hay fever or asthma," unless he be at the same time thoroughly versed in the principles and practice of medicine, more particularly of internal medicine. One should not treat a case of allergic sensitization, but rather a patient with allergy. The dietetic treatment of a tuberculous individual with asthma may well be different from that of an asthmatic patient with peptic ulcer. The advice given a well-to-do

patient with contact dermatitis due to furs may be entirely different from that given a poor woman allergic to the same furs earning her livelihood in the furrier's establishment.

Allergy is but a part of the whole. The ancient Orientals had an intriguing custom of depicting a picture on the panels of a screen in a composite way so that each panel would represent a part of the whole. The complete picture does not appear as a unity, but is depicted as a summation of its component parts represented by the separate panels. George Draper, drawing on this analogy, divides the human constitution into four panels: the morphologic, physiologic, psychologic and immunologic. One might be tempted to add a fifth, the allergic, but, as we shall bring out, this factor of the constitution is so intimately connected with those factors which are usually classed as immunologic, that we may accept Draper's picture as he has painted it, allocating a surprisingly large portion of the immunologic panel to allergy, a portion which blends, with no clear-cut boundary line, into the portion devoted to immunity.

Certainly none would argue that immunity in its broad interpretation is not a fundamental part of the picture of the human constitution. As early as 1907 Victor C. Vaughan suggested that immunity and anaphylaxis (allergy) were different manifestations of an identical mechanism at work within the body.

The treatment of a patient ill with asthma implies much more than the obtaining of symptomatic relief with adrenalin injections, the administration of iodides, or a change in environment. It implies an exhaustive study of those constitutional characteristics which predispose the particular individual to react with etiologic agents in this manner; it implies a comprehensive study of dietetic and other environmental factors which serve as exciting agents in this predisposed individual; and it implies a conscious effort on the part of the physician to relieve the patient insofar as possible from contact with these exciting factors and so to alter his reaction capacity through physiologic readjustment or therapeutic measures that he will no longer respond in an apparently abnormal manner. This often requires most painstaking study and collaborative effort on the part of the physician and patient, sometimes for months or even years. Even then, our efforts may meet with failure; but as a rule failure is due to lack of investigative effort on the part of the physician, lack of intelligent cooperation on the part of the patient, or lack of a correct understanding of the true significance of the allergic response. The first two causes of failure can usually be overcome, and the third will also eventually be conquered.

Some may criticize the apparent complexity of the procedures required in the study of allergy. In a measure this has been an actuality, but will probably become less so as we become increasingly familiar with allergy. We need but recall the extremely complex mechanism first used in the clinical determination of the basal metabolism by indirect calorimetry, with its battery of absorbing jars and great lengths of rubber tubing, as compared with the extremely simple metabolism apparatus in clinical use today.

Today we are still very much in the complex or complicated stages of the study of allergy. This appears, as with other problems medical, to be an essential step in the process of reaching a more general understanding. Simplification will come, based upon knowledge gained by the more intricate methods of study. While this volume, to be comprehensive, must present the minutiae of allergic study, every effort will also be made to include those simplifications which have been shown to be safe short cuts and which do not cloud the issue.

The analysis of the case of a highly allergic patient sometimes requires much time, even months of intermittent study. But if this eventuates in relief it is far better than continued symptomatic treatment over an indefinite period with the eventual development of a hopeless attitude on the part of the patient. Simple cases can be worked out rapidly.

Antiquity.—The antiquity of allergy is uncertain. In an earlier volume I stated my belief that the manifestation is as ancient as man himself, probably more so inasmuch as it affects animals as well as man. Today, I am not so certain, at least as regards its frequency.

Is the apparent increasing frequency of allergic manifestations actual or fictitious? Is food allergy or migraine affecting an increasing percentage of the population, or does this only appear to be so, as a result of our increasing interest in the phenomenon? We can say with reasonable assuredness that the allergic diseases in all probability have existed as far back as the records of history carry us, as far back as civilization reaches. We cannot determine whether allergy was as frequent centuries ago as it is today.

Is it, on the other hand, a disease associated with civilization? Is it, in great measure a product of the artificial environment in which we live? If so, does this artificiality cause the fundamental intrinsic changes which we term the allergic state or the allergic tendency, or does such an environment merely contribute increased and concentrated quantities of the allergic excitant, thereby increasing the actual manifestations of an already present or latent predisposition? Both of these possibilities actually exist.

The antiquity of those symptom complexes which we now recognize as allergic is clouded in obscurity. We do know that Botallus in 1565 described a condition which we recognize today as hay fever or asthma due to extrinsic excitants. We do not know whether he was the first to do so. We know that the term asthma appears in the Hippocratic writings but that it was used as a general term indicating difficult breathing. We know that Bostock, an Englishman, appears to have been the first, in 1819, to describe seasonal hay fever as a distinctive symptom complex and that Elliotson, twelve years later, first suggested that the disease was due to pollens, although offering no substantiating evidence. Migraine was described by Aretaeus about A.D. 100, and again by Galen. We do not know when food idiosyncrasy was first clearly recognized. The old expression, "One man's meat is another man's poison," has been employed by many writers since its first enunciation by Lucretius in the first century B.C.

Any study of the antiquity of urticaria or the allergic dermatoses is confronted by the obstacle raised by the fact that until recently most chronic skin lesions were termed eczema. Indeed, it was not until the advent of modern dermatology that the chronic infections of the skin were separated from the other dermatoses.

Is allergy increasing? Our present interest in the history of allergy is rather in those more recent observations which have led to present understanding of the phenomenon. For this we may most appropriately take Bostock (1819) as our point of departure. Bostock, like so many others who have contributed to clinical allergy, was himself allergic. He suffered from seasonal hay fever and it was no doubt his interest in his own symptomatology that led him to seek out similar cases. The fact that after nine years' search he had seen or heard of only twenty-eight persons afflicted with similar symptoms, and ten other questionable cases, would suggest that hay fever was much less com-



Fig. 1. -Some pioneers in pollinosis.

John Bostock (1773-1846), of Guy's Hospital, London (upper left), who wrote the first modern English physiology (1823) and who, in 1819, first described the disease now termed hay fever.

John Elliotson (1786-1868), of the University of London (upper right), who first employed the stethoscope in England and who, in 1831, suggested that Bostock's summer catarrh depends on the flower of grass, probably upon its pollen.

Philipp Phoebus (1804-1880), of the University of Giessen (lower left), whose monograph (1862) correlated the then known facts of hay fever.

Morrill Wyman (lower right), of the Harvard Medical School, who in 1872 published a monograph on Autumnal Catarrh in which he recognized ragweed pollen as one of the causative agents.

mon in the days of Bostock than today. However, we must realize that grass hay fever even today in the United States is relatively infrequent as compared with weed hay fever and that in England the grasses are the chief causative agents. We must also remember that means of communication being much less extensive in those days, Bostock's circle of acquaintances and list of patients were probably much smaller than those of the average physician of today.

Today we draw our conclusions concerning the wide distribution of the allergic diseases chiefly from community surveys. Unfortunately there are no surveys available for former periods.

The available evidence would suggest that allergy is a more frequent disease in the United States than in the Old World. America has more artifices designed to promote the comfort of the individual than are to be found in Europe. This applies not only to central heating and air conditioning but also to the preparation and preservation of food and many other factors. Arguing on these generalizations one might be tempted to conclude that allergy is a disease of civilization, or better, a disease that depends in part at least on the increasing artificiality of one's environment. One is not as constantly exposed to the vicissitudes of nature in the New World as in the Old. Such a generalized conclusion, however, is fraught with very definite pitfalls.

We have already mentioned that hay fever is much commoner in the United States than in England or on the Continent. But we cannot say that hay fever due to the grasses is more common. And it is the grasses that are chiefly responsible for pollinosis in Europe. The much more toxic ragweed has so far been unable to gain any extensive foothold in the Old World.

Scheppegrell concluded many years ago, from correspondence with physicians of the localities, that hay fever and asthma are much less common in Central and South America than in North America. One would be inclined to conclude that allergy in general is less frequent there and that it might be due to more primitive ways of living. I have, however, made a study of the territory around Mexico City and find that it is quite true that allergy to air-borne pollens occurs less frequently. This is not due to the manner of living but to the fact that those plants which are responsible for so much hay fever in the United States are infrequent in Mexico. Here as throughout the tropics cross-fertilization of plants is accomplished by insects much more than by the wind.

On the other hand, food allergy is not at all infrequent in Mexico City. No doubt a careful survey would reveal as much food allergy there as in cities of this country. Allergy is said to be less frequent in the colored race but I know of no comprehensive surveys that have been made to demonstrate this. I have personally seen many cases of various allergic manifestations in the negro.

Against the suggestion that allergy is a product of civilization is the fact that it occurs in animals. Veterinarians find eczema due to foods to be not an uncommon disease in cats and dogs. They even observe asthma. Bray has described hay fever among cattle. But these are all domesticated animals living in what to them is an artificial environment.

One cannot prove at the present time from a study of persons in different parts of the world, in different environments, in different economic or social groups, or with different manners of living, differing basic diets or culinary customs, that allergy is increasing with the increasing artificiality of civilization.

Our artificial environment. I am increasingly intrigued with the conception of a possible relationship between 'civilization' and allergy. What observations suggest such a possibility? The statement has been made that the

allergic child is above the average in intelligence. If this should be true, it might be inferred that this is associated with a more cultured and therefore possibly more artificial environment, although such does not necessarily follow.

Suggestive is the observation that persons may become sensitized to rather highly refined substances. Much of what we eat has gone through such a preliminary process of refinement that it is almost an altered food. I have seen patients sensitized to patent wheat flour, that which most of us eat, who find that they can eat whole wheat bread without symptoms. The protein of white flour is still wheat protein, but it is conceivable that some protective substance which diminishes the tendency to sensitization has been removed with the wheat germ and the bran. This is, for the present, merely supposititious. The argument might be reversed; cooked apples are less likely to cause symptoms than uncooked, although certain persons tolerate raw apples, but not plain applesauce.

We are perhaps on slightly firmer ground when we reach a consideration of physical allergy, especially sensitization to heat or cold. Although the writer, living on the Eastern Seaboard, has not observed physical allergy playing as important a part in the symptom complex as has been described by Duke in the Midwest, we have nevertheless seen quite a large number of individuals who were clearly sensitive to the effects of heat or cold. Some have reacted with allergic symptoms, asthma, hay fever, urticaria, while others have responded only with an exaggeration of those symptoms which normally occur after prolonged or heavy exposure. The former may be considered allergic, while the latter are suffering from poor adaptability to environmental changes.

In any event, the evidence suggests that in maintaining ourselves in a relatively constant temperature environment, with the temperature of spring-time prevailing in our homes and in our places of work throughout the four seasons, and with adequate protection against cold, in clothing and closed automobiles, we are gradually losing the ability to acclimatize ourselves to sudden or extreme temperature changes. The more susceptible among us are therefore likely to react with symptoms following such changes.

The frequency of sensitization to new and artificial synthetic drugs is most interesting. Clear-cut allergies to dinitrophenol, sulfanilamide, iodides, arsphenamines, aspirin, amidopyrin and the synthetic hypnotics, are cases in point. Allergy to dinitrophenol had become manifest in a considerable number of cases before this drug had been in use for even twelve months. Often, indeed, only a few exposures to these completely new and foreign chemical substances are required before allergy to them develops.

No conclusion whatsoever can be reached at the present time concerning these interesting observations. Rather, they are recorded to illustrate, not so much the complexity of the problem, as its extreme interest and the possibilities inherent in constructive study of the subject.

Some problems for consideration. We have today gone far beyond the earlier concept of allergy as being limited to protein sensitization and must recognize it as a type of reactive response to contact not only with proteins but with oils, polysaccharides, even inorganic chemicals, and environmental factors such as heat, light and cold.

If, as is generally stated, ten per cent of the population manifest frank or outspoken allergy and if upwards of an additional fifty per cent show some minor allergic manifestation at one time or another, then allergy becomes almost the rule rather than the exception. One is inclined to inquire whether allergy should be considered as a disease or whether it is almost a normal

condition. This question has been weighed by Rackemann and by Vaughan who conclude that the allergic reaction is in great measure an exaggeration of a normal physiologic response.

One could scarcely say that allergy is not a disease, but surely if it may affect half the population and if it is primarily a functional disturbance, which after its disappearance allows a prompt return to a normal metabolic state, then it seems reasonable to assume that the solution to the riddle of allergy will ultimately be reached through a study of the normal physiologic mechanism.

Why do some persons become allergic? Granting that they are allergic because they have become sensitized to some substance through prior exposure, why did they become sensitized? Granting an undoubted hereditary tendency, why did they react in this way to an exposure or contact which gives rise to no such reaction in other persons? We have theories of the mechanism of allergy and descriptions of the phenomena of the disease, but we really know very little indeed of why some people do become allergic.

Granting that for some reason certain persons do become allergic or sensitized to environmental substances, what factors determine the allergen? We are accustomed to say that the extent or duration of exposure plays a part. Thus one is more likely to become allergic to those foods with which one comes into frequent or prolonged contact. Wheat, egg and milk are found to be the three commonest allergenic foods for persons with frank or major allergy. Even here, however, the answer is not so simple. One may argue that a person becomes sensitized to wheat because one has the allergic tendency, and one is so constantly exposed to wheat. However, the exposure to egg or milk is often just as extensive, sometimes more so. And yet a patient may be sensitized to wheat and not to egg or milk, or vice versa.

Furthermore, it is not alone those substances with which one comes into prolonged contact which cause sensitization. One is especially likely to become sensitized to substances with which there is only occasional or rare contact. This is true of many of the drugs and foods such as strawberries, onions, tomatoes, cucumbers, melons, cabbage. Under certain circumstances it would appear that substances with which one comes into contact only rarely are especially prone to cause sensitization. We will discuss this at greater length elsewhere.

This is likewise true in experimental allergy. Ragweed is the commonest pollen causing allergy in this country. Apparently a person with an allergic tendency easily becomes sensitized to ragweed. Yet, attempts to sensitize man intentionally, even allergic man, to ragweed pollen by parenteral inoculation have not met with success. On the other hand it appears extremely easy to sensitize man intentionally to rabbit serum or guinea pig serum. Why is there this difference?

It is generally agreed that the skin test method of identifying allergenic substances is a great diagnostic aid. Skin reactions to the common inhalant allergens give reliable information, while positive reactions are observed to foods which fail to cause trouble and negative ones to foods which are very clearly responsible for symptoms. Why is there this difference in the manner of the skin response?

These are some of the many questions which remain as yet unanswered. The complexity of the problem that make it a stimulating and intriguing field for investigation. I shall certainly not attempt to answer all of them in this volume because for many of them there is as yet no answer available. At the same time any theory which helps to rationalize the subject is worthy of presentation even though its originator realizes that a theory based upon only that portion of the

facts which today are available will be quite likely to go into the discard, as the discovery of new facts gradually broadens our knowledge and clarifies our understanding. This is precisely the function which theories should serve. The theories of a day serve as stepping stones on which one may advance to a place where eventually the perspective is clearer. The intermediate stones are necessary. The theories explanatory of experimental anaphylaxis are very appropriate instances of this fact. Possibly a dozen theories contributed by men of great ability have been seriously studied from time to time. None of them is accepted in its entirety today and yet they have been necessary steps in the evolution of what we now know of the subject. For this reason I have no hesitancy in incorporating my own explanatory hypotheses in this volume, especially when they appear to me to clarify present knowledge of the subject.

CHAPTER II

HISTORICAL

Bostock first described a form of catarrh which occurs only at certain seasons of the year and which he believed should be placed in a separate disease category. Blackley, many years later, presented convincing evidence (1873) that this symptom complex, including seasonal hay fever and asthma as well, is due to exposure to the pollen from certain plants. One might have anticipated that this would have been graded as a discovery of the first order and worthy of the plaudits of the scientists of the day. However, Blackley's observation received scant attention, for two reasons. First, there was no explanation why certain persons should experience illness from contact with pollen while the majority of persons could stand exposure with impunity. If pollens produced symptoms in certain individuals, they should in all. At that time food idiosyncrasy was recognized, but a connection between the two was not clearly seen.

Second, granting Blackley's observation as correct, it presented nothing new in the field of therapy. Assuming that pollen may be responsible in some obscure way for seasonal hay fever and asthma, what was to be done about it? It was recognized that a sea voyage or sojourn at the seashore often gave relief, and presumably as many as could arrange it were already availing themselves of this benefit. Blackley's theory offered nothing new in treatment.

Antivenins and antitoxins. A new idea in treatment had, perforce, to await an entirely new concept in medicine which was ushered in by the pioneer investigations of Henry Sewall (1882-1889) on snake venom. Sewall carried on his studies in the physiology laboratories of the University of Michigan, where he showed conclusively that pigeons could be immunized against the venom of the rattlesnake. This made possible our present understanding of toxins, antitoxins, anaphylaxis and, indeed, allergy.

Calmette, in Paris, having observed Sewall's report, attempted to ascertain how the pigeons became immunized. As a result he succeeded in producing an antivenin which would protect exposed animals against the toxic effect of snake venom.

The next personage of importance to appear in this brief story of the evolution of allergy is Roux. Pasteur's right-hand man contributed his portion by demonstrating that diphtheria toxin is similar to the snake venom in the manner of its poisonous action. Von Behring carried on, by producing reactions with diphtheria toxin similar to those that had been produced by Calmette with snake venom. He manufactured diphtheria antitoxin and demonstrated its efficacy in therapy.

We now had evidence that a poison of animal origin might be toxic and that an antivenin might be made which would counteract its toxic activity; that a similar toxin could be produced by bacteria, against which therapeutic antibodies could be produced. Ehrlich soon showed in his experiments with ricin that the same might be true in the vegetable kingdom.

Pollantin and graminal.—Here was a new field of medicine, a new method of therapy. It was but a logical step from this to the attempt by Dunbar of Hamburg, Germany (1905), to produce an antitoxin which would counteract the poisonous element in pollen. Dunbar accepted Blackley's contention that



Fig. 2.—Some pioneers in the study of toxins and antitoxins, who paved the way for later research in anaphylaxis and allergy.

Henry Sewall (upper left), of Ann Arbor, whose successful immunization of pigeons against snake venom was followed by the production of antivenin by *Albert Calmette* (lower left), of Paris.

Pierre Roux (upper right), of the Pasteur Institute, showed that diphtheria toxin acts in a manner similar to that of snake venom. Applying these facts, *Emil von Behring* (lower right), of Germany, developed diphtheria antitoxin.

hay fever was due to pollen and postulated that the causative factor was a toxin secreted by the pollen. He therefore manufactured an *antitoxin* by injecting pollen from the cereal grains, into horses. This had been successful in the snake venom and diphtheria toxin experiments and he saw no reason why it should not be equally efficacious in pollinosis. The serum from animals so treated was marketed under the trade name *Pollantin* and was sprayed, for local effect, upon the nasal mucous membranes of large numbers of hay fever sufferers. There were two reasons why this was predestined to failure. First, if soluble toxin was actually secreted by the pollen cells, *all* persons instead of a minority of the population would have suffered. Second, as was later shown, no such toxin is formed or secreted.

Weichardt, accepting Dunbar's theory, concluded that if an antitoxin can be formed by the injection of pollen into cattle, it may be produced more easily by feeding the pollen. He therefore marketed *Graminal*, normal serum from cattle which had been fed large quantities of grain containing pollen.

So we see that one of the first major developments in experimental medicine after the time of Blackley was applied to the treatment of seasonal hay fever and asthma. Unfortunately it was unsuccessful.

Anaphylaxis.—The next major development was that of anaphylaxis; this is intimately associated with the evolution of antitoxin.

Magendi in 1839 had observed that rabbits, when injected repeatedly with dog serum, sometimes manifested unaccountable reactions following reinjection. Likewise Flexner in 1893 made similar observations and Theobald Smith some years later described this phenomenon to Ehrlich who later discussed it as "The Theobald Smith Phenomenon." But, in the discussion of anaphylaxis, credit can go to none of them, since none attempted to explain the observations.

Credit for this must go to Richet and his associates (1898-1902). Richet, while sojourning with the Prince of Monaco on his yacht in the Indian Ocean, undertook a study of the toxic or urticating substance of the Portuguese man-of-war, a variety of jellyfish. The investigations being incomplete upon his return to France, he continued them with the sea anemone, a variety of *stinging nettle*. Richet, working upon the theory that the urticating principle is a toxin, injected anemone extract into dogs. To his surprise he found that the same extract which had proved entirely innocuous on first injection, sometimes proved severely toxic, even lethal, on reinjection after an interval of several days. Here was a curious phenomenon. It was not entirely new. Flexner and Smith had described it and undoubtedly many others had observed it. The phenomenon was indeed becoming very much of a commonplace, since the advent of diphtheria antitoxin.

For the standardization of antitoxin, guinea pigs were being inoculated with a mixture of toxin and antitoxin. It soon became apparent that pigs once used as test animals were no longer reliable for subsequent testing, because a surprisingly large proportion of them would unaccountably die following repeated injections of the horse serum. These were *changed guinea pigs*. They reacted to a given stimulus in a different manner from normal animals. Similar observations were being made in the clinics where at times persons experienced sudden alarming symptoms following the injection of diphtheria antitoxin. To the majority of workers this was a curious phenomenon. To Richet and his associates, Héricourt and Portier, it was an unanticipated incident, requiring explanation. They abandoned their study of the urticating substance and devoted their efforts to an explanation.

By 1902 they had completed much of their investigation and had propounded their theory. The two basic concepts which they proposed at that time hold true today. (1) *A foreign substance which on first injection may be relatively harmless may, on reinjection, become severely toxic, even fatal, when given in the same or even smaller dosage.* (2) *An interval of several days must elapse between the first and second injections.*

They believed that during the interval some change had taken place within the tissues of the body. According to their concept some protective mechanism had been destroyed or removed, thereby rendering the animal hypersusceptible to the toxic action of the original substance. We should bear in mind that they were dealing with a primarily toxic (urticating) substance and that they believed that there was a toxic action of the primary extract against which the body normally protected itself. They thought in terms of immunity, a subject just then very much to the fore.

Richet's conception of the destruction of a normal or natural immunity factor during the ten-day incubation period justified his selection of *anaphylaxis* ("lifting up of protection," or "removal of protection") as a descriptive term. This was contrasted with *prophylaxis* or "favoring protection," a word much in vogue at the time in discussions of immunology.

It remained for Arthus (1903) to show, in his demonstration of the familiar Arthus phenomenon, that a substance which is completely nontoxic, such as dog serum, may produce comparable results.

Even though Richet was in error in believing that the anaphylactogenic substance must be primarily toxic, his postulates still hold with nontoxic substances, and he may be looked upon as the founder of experimental anaphylaxis.

Rosenau and Anderson (1906) in the United States and Otto (1905-6) in Germany contributed the most important of the early details, facts which still hold and which form the basis of our concepts of anaphylaxis. They demonstrated that this phenomenon was entirely different from that of toxin and anti-toxin formation; they discovered and described the condition of antianaphylaxis which followed repeated small, subtoxic injections of the antigen; demonstrated that the incubation period is about ten days; that the reaction is specific; that sensitization may be transferred in utero from mother to offspring and that a great variety of possible antigens, animal, vegetable and bacterial, might be responsible.

Allergy.—The term allergy was suggested in 1906 by Pirquet who took exception to the too descriptive term, anaphylaxis, as compelling one to subscribe by its use to a theory which was not yet proved. He preferred *allergy* as being nondefinitive and indicating only a state of altered response, altered energy or altered reactivity. This term, describing as it does what has happened without implying a theory of rationalization, is undoubtedly more acceptable. Some modern writers on allergy have objected because Pirquet implied that he believed that an antigen-antibody reaction occurs in the anaphylactic or allergic response. Recent clinical work has cast some doubt on this, indicating that clinical allergic reactions may take place in the absence of an antigen-antibody reaction. However, Doerr, working with Pirquet, elaborated the latter's definition to include all forms of altered reactive capacity, irrespective of the presence or absence of antigen-antibody reaction. With this understanding the term allergy is entirely appropriate today in the description of all of the so-called clinical allergic responses.

Clinical allergy.—Bostock first described hay fever. Blackley demonstrated its relationship to pollens as an etiologic factor. Dunbar and Weichardt failed

to solve the problem of pollinosis on the basis of the new theory of toxins and antitoxins. But here was yet a newer theory. To Weichardt (1905) and Wolff-Eisner (1906) goes credit for first suggesting that hay fever may be an anaphylactic phenomenon. Wolff-Eisner's attempts to prove this were not clinically conclusive but no doubt served as stepping stones for future progress. When Auer and Lewis (1910) described the outstanding pathologic picture of anaphylactic shock in guinea pigs as that of bronchospasm, Meltzer (1910) suggested that by analogy bronchial asthma might be an anaphylactic disease.

In the meantime Noon of London had actually undertaken the treatment of pollen hay fever by the preseasonal injection of minute but increasing dosage of an extract of the offending substance, in an effort to produce a state comparable to that described by Rosenau as antianaphylaxis.

With the publication of his successful results (1911) we can establish the beginning of clinical allergy. Many disease phenomena have been added to the picture since Noon's original investigations on pollinosis. The historical development of the various allergic symptoms will be reviewed in their proper sections.

CHAPTER III

THEORIES OF ANAPHYLAXIS

In Richet's early investigations on the urticating substance in sea anemone he believed he was dealing with a primarily toxic agent. This was so mildly toxic that on first injection it caused no symptoms. The body possessed some mechanism favoring protection, prophylactic, which counteracted toxic activity. But the first injection caused some change in the body which resulted in the removal of this normal protective mechanism. For this new state Richet coined the term anaphylaxis, *without protection*.

Soon, however, Arthus demonstrated that the same phenomenon occurs when the substance injected is in no way primarily toxic. Horse serum is an example.

It was but natural that the new Ehrlich side chain theory should be utilized in an attempt to explain this curious phenomenon. It had been used successfully in promoting an understanding of the basic processes of immunity. The terms antigen, antibody, free receptors, sessile receptors and complement were well understood. Victor C. Vaughan who had been carrying on extensive investigations in bacterial immunity, found that animals could be sensitized to bacterial proteins as well as to the proteins of horse serum, egg white, etc. Similar conclusions were reached by Rosenau and Anderson. Prior to this, major interest in bacteria had dealt with problems of immunity. Vaughan suggested (1907) that anaphylaxis and immunity both depended upon the same fundamental process. This theory is now generally accepted. The terminology of immunity was applied to that of allergy.

Reaction site is in the tissues. Early theories were based on the assumption that the reaction between antigen and antibody takes place in the blood stream. Soon, however, convincing evidence was produced that the site of reaction is in or on the tissue cells themselves. Thus the *humoral theory* was supplanted by the *cellular theory*.

Friedemann and Otto as well as Doerr and Russ showed that in the process of *passive sensitization*, in which the blood of a sensitized guinea pig is transferred into a normal nonsensitive guinea pig, the latter does not become sensitized until after an interval of at least four hours. Indeed twenty-four to forty-eight hours must elapse before maximum passive sensitization has been accomplished. This interval is presumably required for the antibodies to become firmly attached to the tissue cells.

Doerr further showed that the intensity of passive sensitization increased as the passively transferred antibodies progressively disappeared from the blood stream. The highest degree of reactivity appeared when the injected antibody was nearly entirely out of the blood.

Manwaring bled actively sensitized dogs, replacing the blood with that from nonallergic dogs, finding that even though the antibodies were thus removed from circulation the animals remained as highly sensitized as previously.

Schultz (1910) washed strips of sensitized intestinal smooth muscle free from blood, after which he found that contact with the specific antigen caused an anaphylactic response, with muscular contraction. Dale improved upon the Schultz technique, developing the uterine strip method which has since become a



Fig. 2. —Some pioneers in the study of anaphylaxis and allergy.

Charles Richet (upper left), of Paris, first systematically investigated the phenomenon, proposed an explanatory theory, and coined the word anaphylaxis.

Milton Rosenau (upper right), when serving as Director of the Hygienic Laboratory in Washington, established, with Anderson, the major fundamental facts of anaphylaxis.

Victor Vaughan (lower left), of Ann Arbor, by early work on bacterial theory did much to establish the concept of an integral relationship between allergy and immunity and formulated the theory of "protein poison," probably the most widely accepted of the earlier theories in the United States.

Clemens von Pirquet (lower right), Viennese physician, coined the term allergy and contributed much to our knowledge, especially with regard to tuberculin allergy.

routine procedure in the study of sensitization. He, too, found that these tissue cells when freed from blood are still capable of reacting anaphylactically.

These were the fundamental observations which gave convincing evidence of the cellular site of the anaphylactic reaction.

Circulating antibodies confer protection, immunity. -Weil (1911) found that sensitized guinea pigs could be partially protected against anaphylactic shock by the preliminary injection of large amounts of immune blood just prior to reinjection of the antigen. Presumably the reinjected antigen came in contact with and was neutralized by the circulating antibodies which had not yet become fixed to tissue cells.

These and similar observations have been the basis for the concept that if an antigen is introduced into the blood stream, in the absence of protective *circulating* antibodies, the antigen will combine with the *sessile* antibodies attached to the sensitized tissue cells, thereby damaging the cells and producing an anaphylactic reaction; but that if there are free antibodies in the blood, the antigen will first combine with them, a process which obviously protects the tissue cells. The former reaction is that of anaphylaxis, the latter that of immunity.

Nature of antibodies.—Heidelberger and Pedersen (1937) state that antibodies are actually modified serum protein. The electrophoretic properties of antibodies as shown by Tiselius and Kabat (1939) identify them as modified globulin in the so-called gamma globulin fraction. Some antibodies have a molecular weight very close to that of the serum globulins, while others may be very much larger. Buchner's theory of antibody formation has been abandoned. Breinl and Haurowitz (1930) suggested that, under the influence of the antigen, the globulin was so modified that it reacted with the antigen on subsequent meeting. Pauling (1940) believes that the antigen so modifies the end groups of the globulin molecule that they can specifically react with the antigen when the end groups break off and are free. Sabin (1939), using a red dye, found it entering the macrophages. These cells produce a wavy surface film which is cast off and which she believes may be modified by the antigen which entered the cell, and this modified surface film is antibody globulin.

None of these theories is entirely satisfactory, and none is generally accepted.

Site of the reaction. Unfortunately the process is not so simple as the side-chain theory would indicate. There is much more not known concerning the mechanism of anaphylaxis than is known. One fact which seems to be definitely established is that the reaction is cellular, in the tissues rather than in the blood stream. Even today there is no certainty as to what tissue cells are involved, whether it is a general reaction affecting many organs or tissues, or whether a special type of cell is involved. Considerable evidence, however, points to the cells of the reticulo-endothelial system, especially those of the liver, as playing an important role. Furthermore, there is no unanimity as to what occurs to the cells during the reaction. Some believe that the reaction occurs on the surface, others that it is intracellular. Some believe that the reaction is chemical, with the liberation of a specific poison, others feel that it is physical, associated with colloid changes on the cell surface.

The reticulo-endothelial system has been mentioned as a possible site of the reaction. This system can be rendered partially inactive by the vital injection of India ink or trypan blue, substances which are selectively taken up by the cells. With the system thus blocked, it has been shown that antibodies are produced in smaller quantities and that the intensity of the anaphylactic reaction is diminished.

Increased capillary permeability.—The endothelial cells of the capillaries certainly participate in the reaction, although here as in the reticulo-endothelial system we cannot conclude that evidence of participation is necessarily evidence that this is the site of the fundamental reaction. The allergic response is accompanied by increased capillary permeability, sometimes of high degree. Thus Manwaring found that perfusion of the isolated lung from a sensitized animal, with solution containing the antigen, resulted in such increased capillary permeability that 75 per cent of the perfusate was lost in its passage through the lungs, being diverted through the hyperpermeable capillary cells into the lung tissues and spaces.

Smooth muscle spasm.—The other striking reaction is that of smooth muscle spasm. The localization of the anaphylactic reaction in guinea pig, rabbit, and dog is the bronchial musculature, the pulmonary circulation, and the hepatic veins, respectively, and is dependent upon the localization of smooth muscle in these tissues. The Schultz-Dale reaction using intestinal or uterine strip illustrates this reaction.

Liver.—Manwaring concludes from his studies of anaphylaxis in dogs that the liver plays an important part and suggests that the antigen stimulates the liver cells to react with it, with the formation of an anaphylatoxin-like substance which, carried through the blood, produces the other changes in the capillaries and smooth muscle.

Broh-Kahn and Mirsky (1937) have shown that removal of the liver, spleen and other abdominal viscera in guinea pigs will not prevent anaphylactic shock on subsequent reinjection of the antigen.

In short, there is experimental evidence indicating that these four groups of tissues play a part in the allergic response (*capillaries, reticulo-endothelium, smooth muscle, liver*) but there is no certainty as to just what part each plays or whether their responses are primary or secondary.

Physical theories.—One of the most generally stressed reasons for the consideration of a physical theory is the rapidity of the response. Anaphylactic shock in human beings as in animals is often very prompt, but it is especially in the uterine strip procedure that it is seen to be almost instantaneous, the uterine muscle contracting promptly upon contact with the antigen. Protagonists of the physical theory maintain that if a chemical poison were at work, there should be more of a lag between the contact and response, due to the time required for penetration of the cells. The physical theories involve colloid chemical changes, usually considered as being on the cell surface, thereby disrupting normal cell processes. An early suggestion was that of precipitation of some substance on the cell surfaces. This might be considered analogous with the precipitin reaction, an immunologic phenomenon which may be observed in vitro. Deposition of fibrin upon the cells has been suggested. Colloid changes in ferments and antiferments have been suggested.

Wells states, "The fact that slight disturbances in the equilibrium of plasma colloids render them highly toxic is an outstanding fact, and it becomes easily understandable that a similar alteration in colloidal equilibrium within the cell protoplasm may produce equally profound intoxication of the cell, so that at present there is a growing tendency to seek an explanation of anaphylaxis in the domain of colloidal chemistry."

Chemical theories.—There have been many theories of the chemical factors responsible for the reaction, including Friedberger's *anaphylatoxin*; Victor Vaughan's *protein poison*; Dale and Laidlaw's *histamin*. The most recent is that of Sir Thomas Lewis who suggests the formation within the tissues of a toxic histamine-like substance, designated *H-substance*. This is based on his study of the formation of urticarial wheals. A histamine-like substance may be extracted from such reacting tissues, which produces contraction of the uterine strip and other responses similar to those caused by histamin. He conceives of the *antigen* as *reacting with tissue cells*, with the resultant *production by the cells of H-substance which*, when liberated, *irritates the capillary vessels* with resultant increased capillary permeability.

Discussion.—While we remain ignorant of the actual physical or chemical processes at work in the production of anaphylactic shock, the evidence favors the conclusion that the reaction takes place in or on the tissue cells themselves; that four groups of tissues play a particularly important part, the reticulo-endothelial system, the capillaries, smooth muscle, and the liver; that we do not know whether the reaction of any or all of these tissues is primary or secondary; and that the bulk of evidence indicates that the poison responsible for the reaction is formed within the body, due to physical or chemical changes in some constituents of the serum or cells themselves, rather than from the breakdown of the antigen with consequent liberation of some poisonous substance contained in the antigen.

If we are to assume that clinical allergy and experimental anaphylaxis have a common pathologic basis, observations and theories of the nature of anaphylaxis are applicable to the study of clinical allergy. Fortunately, although the *mechanism* of experimental anaphylaxis is incompletely understood, the *phenomena* of it are a matter of record. So many of these facts have been studied that the clinician can proceed with reasonable assurance, knowing how his patient will in all probability react to a stated allergenic exposure. At the present stage we know much more about what an allergen does than how it does it.

Progress in clinical allergy has been based upon knowledge of the phenomena of experimental anaphylaxis. We have hurdled the hiatus of a complete explanation. It may be long, indeed, before the complete explanation is made. On the other hand it may develop that a clearer understanding of the facts of clinical allergy may furnish the clue which, when applied in experimental work, will bring us nearer to an explanation.

CHAPTER IV

EXPERIMENTAL ANAPHYLAXIS AND CLINICAL ALLERGY

Points of Dissimilarity

This branch of medicine is an outgrowth of certain unique laboratory observations grouped under the general heading of experimental anaphylaxis. At first only hay fever and asthma, together with reactions that occasionally occur after the administration of therapeutic serum, were classed as anaphylactic or allergic. Soon urticaria was added to the list, followed shortly by food allergy and gradually by a number of other symptom complexes.

Some very competent investigators, led by Coca, seriously questioned the identity of experimental anaphylaxis with clinical allergy, insisting that the two could not be basically the same. The three chief reasons propounded were that experimental anaphylaxis is an antigen-antibody reaction, while antibodies are usually not shown to be present in clinical allergy; human allergy is an hereditary manifestation transmitted from parent to offspring in accordance with Mendelian law, while experimental anaphylaxis cannot be transmitted except passively from mother to fetus and then only in the one generation; animals may be experimentally sensitized with great facility, while it is difficult, almost impossible, to sensitize human beings intentionally.

The interesting feature of this development is the paradox introduced by the reversal of the usual method of study. It has been many years since Roger Bacon and William Harvey first applied the experimental method. Since then it has been responsible, more than all other procedures, for advance in medical science. Given a certain human disease complex, be it cardiovascular, nephritis, diabetes, poliomyelitis, or what not, a more intimate understanding of its pathogenesis, pathology and, eventually, treatment is reached if we can reproduce the disease or a disease very much like it in animals. Once this has been accomplished, we are in a position to proceed with studies which cannot be made on human beings. Dogs are rendered diabetic, monkeys are infected with the virus of poliomyelitis, guinea pigs are made tuberculous and rabbits are rendered nephritic. Subsequent studies have added much to our knowledge of these diseases. Rarely is experimental pathology produced entirely similar to that of the human disease, but it is sufficiently like it to facilitate productive research. Analogies are recognized and conclusions drawn. Differences are understood as due to the difference between natural processes and experimental procedure.

In allergy the situation has been reversed. Animal experimental work preceded clinical recognition. This is readily understood since allergy as we know it today is not limited to a single organ or tissue but involves a variety of tissues throughout the body. Furthermore the pathologic changes are chiefly transient, reversible, quite different from those irreversible structural changes in organs and tissues which may be studied at leisure postmortem. Had the allergic response been limited to one organ and accompanied by permanent structural changes, experimental studies would undoubtedly long since have been applied.

A curious, heretofore unrecognized, laboratory phenomenon had been studied long before the suggestion was made that a series of clinical symptoms might be based upon a similar etiology. In spite of the fact that the major portion of our recent progress in clinical allergy has been based upon its analogy with experimental anaphylaxis, some investigators deny a relationship, chiefly, I believe, because they are so much more conscious of the dissimilarities than of the obvious similarities.

Points of Similarity

What have we derived from experimental anaphylaxis that has been of use in clinical allergy?

First is the character of the anaphylactic reaction in animals, which through its similarity to certain human disease manifestations of unknown causation first suggested the possibility that the latter were due to a phenomenon comparable to anaphylaxis. The importance of smooth muscle spasm in anaphylaxis, as described in the bronchospasm of anaphylactic guinea pigs by Auer and Lewis (1910), has its counterpart in many phases of the clinical allergic picture. This justified the suspicion that asthma might be a similar manifestation but could scarcely be used as a logical argument for the inclusion of mucous colitis, urticaria, migraine and eczema.



Fig. 4.—*John Auer*, of New York, whose demonstration that bronchial spasm is an important part of the picture of anaphylactic death in guinea pigs led Meltzer to suggest that asthma may be an anaphylactic disease.

The observation by Schultz (1910) that intestinal muscle, and by Dale (1913) that uterine muscle of guinea pigs responds, with contraction, to contact with the sensitizing agent, suggested the possibility that smooth muscle contraction elsewhere in the body than in the bronchioles might color the picture.

Anaphylaxis in different animal species.—It was then found that different animals react differently.

Auer, Coca, Arilia and others have shown that in rabbits the site of local anaphylactic response is in the pulmonary circulation. In these animals, in

contrast to guinea pigs, the lungs are collapsed at autopsy and there is evidence of an increased resistance to blood flow through the pulmonary circuit. Death is due to right cardiac failure secondary to this pulmonary obstruction. Here, the smooth muscle spasm occurs in the blood vessels of the lungs.

The original investigations of Richet and Portier (1902) were made on the dog. The pathologic physiology in this animal is altogether different from that of the guinea pig or rabbit, consisting of pronounced drop in blood pressure, extreme engorgement of the liver and splanchnic vessels, increased capillary permeability, and heart block. Simonds and Brandes (1924) find unusually large amounts of smooth muscle in the hepatic veins of dogs and believe that the picture of shock in these animals is the result of increased pressure in the hepatic veins caused by contraction of the smooth muscle of its walls.

Kabler and Sherwood (1933) observed that in the anaphylactic cat the blood pressure falls, temperature becomes subnormal, pulse rate is slowed, and there is an increased intraintestinal pressure, suggesting smooth muscle spasm in the intestines. At the same time the kidney volume is decreased, suggesting constriction of the renal blood vessels.

The reaction in the rat is similar to that in the dog (Crocker and Parker, 1924).

The muscle of the heart appears to play a part in frog anaphylaxis. Friedberger and Mita (1911) reported a slowing of the heart. Goodner (1926) found evidence of local sensitization in the organ. Exposure of the sensitized excised heart to the antigen was followed by an abrupt fall in amplitude and some decrease in rate of the heart beat. Wilcox and Andrus (1938) showed a reduction in the rate of flow through the coronary vessels of the isolated guinea pig heart, following exposure to the antigen.

A local response occurs in the heart in turtles, consisting of bradycardia, prolonged diastole, decrease in amplitude, cardiac engorgement, the response resembling that which follows vagus stimulation (Sherwood and Downs, 1928).

In chickens there is pronounced slowing of the heart, with final cessation in diastole (Sherwood, 1928). In pigeons the reaction occurs in the smooth muscle of the crop (Hanzlik, 1927). In the horse and in cattle the anaphylactic response is chiefly intestinal, with diarrhea. Urticaria has been described as part of the experimental picture in the horse, cow and the monkey. A preliminary increase in blood pressure is observed in the guinea pig and the rabbit. This is followed by a pronounced fall. Prolonged clotting time has been observed in the guinea pig, dog and rabbit. Leukopenia occurs in the guinea pig, dog, rabbit and pigeon. Pronounced increased capillary permeability with resulting edema occurs in most animals.

Eagle et al. (1937) find that the delayed coagulation in anaphylactic rabbits and dogs is associated with increase in blood antithrombin. The antithrombic activity increased 100 times above normal. Fibrinogen content of the plasma was not significantly affected. The platelet count was decreased but not enough to delay coagulation.

Doerr found the guinea pig the animal by far the most susceptible to anaphylaxis. Man was considerably less reactive, but even so followed guinea pig in degree. Other animals in order were rabbits, sheep, goats, horses, fowl, pigeons. Dogs and mice are very resistant. The hearts of cold-blooded animals such as the frog react readily to anaphylaxis.

Functional pathology of allergy.—The two most striking components of the anaphylactic picture in all animals are smooth muscle spasm and increased capillary permeability. In the three animals that have been most exten-

sively studied, the guinea pig, rabbit and dog, there are anatomical differences which explain in part at least the differing responses. In the guinea pig the musculature of the bronchioles is especially well developed. In the rabbit there is a similar prominent development in the musculature of the pulmonary artery, while in the dog the same picture is observed in the hepatic vessels.

From the studies of experimental anaphylaxis in different animals we see evidence that the response may occur in almost any organ of the body, especially where there is smooth muscle. Since this includes the vasculature it implies almost the entire body. There is experimental evidence of involvement of the bronchi, the pulmonary circulation, the liver and portal circulation, the stomach, intestines, kidney, bladder, skin, the heart, blood pressure, and even constituents of the blood. An analogous condition has been described in the laboratory for practically every clinical allergic manifestation. Even epilepsy has found its experimental counterpart in the work of Davidoff and Kopeloff. These authors, using dogs, introduced the antigen (horse serum or egg white) onto the surface of the brain in collodion sacs, or injected it directly into the brain tissue through a previously prepared trephine opening. This represented the sensitizing contact. The second contact was accomplished intravenously after the usual interval. Following the intravenous injection, convulsive seizures occurred, on the side opposite to that side of the brain which had been locally sensitized. Control animals which had received intracerebral injections of saline or the application against the brain substance of collodion sacs containing saline failed to react. This evidence strongly suggests the occurrence of local cerebral anaphylaxis, at least in the dog.

Treatment, antianaphylaxis, desensitization. Experimental anaphylaxis has therefore made possible an understanding of the pathological physiology in the different manifestations of clinical allergy. Laboratory research likewise provided the key to successful therapy.

Rosenau and Anderson, as well as Otto, in their early work (1906) observed the phenomenon which was later termed *anti-anaphylaxis* by Besredka and Steinhardt. If a sensitized animal is given a sublethal reinjection of antigen, he will react, but will recover. Thereafter, for a varying period, further injections of the antigen will produce no symptoms. The sensitized animal appears to have been desensitized.

If a much smaller first reinjection is given to a sensitized animal the desensitization may not be complete. The animal will react to the second reinjection, but more mildly. The animal which appears to be most completely desensitized is the one which received the large desensitizing dose, more nearly approaching a lethal one. This procedure is indeed that which was first employed by Noon and has since come into general use in allergic desensitization. It is true that clinically, desensitization is rarely as complete or effective as it may be in experimental animals, due to the fact that great caution must be used in avoiding too near an approach to the lethal dose. Instead of a single desensitizing injection, the safer clinical procedure consists then in repeated injections of gradually increasing amounts of the antigen or allergen. This may be done slowly as in preseasonal pollen desensitization or much more rapidly, as in the procedure of desensitization to horse serum. The more rapidly the dose of antigen is increased, the greater is the danger of systemic reaction.

It seems probable that if one were able without danger to inject a single large sublethal dose, clinical desensitization would be more complete and relief

consequently more effective. Some confirmation is seen in the occasional patient who unexpectedly develops a constitutional reaction. Not infrequently such a person, developing a reaction just prior to or during the hay fever season, will remain free from symptoms throughout the remainder of the season even though no further treatment be given. Although such therapy may be more efficacious, it cannot be recommended because of the hazard involved.

We are accustomed to speak of desensitization in clinical allergy as well as in experimental anaphylaxis. Since, as has just been brought out, a complete state of antianaphylaxis or desensitization is rarely brought about clinically, a much more appropriate term would be that suggested by Cooke, *hyposensitization*. Under any circumstance we are not actually desensitizing. Although the experimental animal or the human subject is for a time less responsive he is still sensitized.

Clinical allergy in terms of Ehrlich's side-chain theory. In the present terminology of immunity and anaphylaxis, a person is immunized against an antigen when there is an abundance of free antibodies in the blood which will combine with the reinjected or reintroduced antigen, thus protecting the living cells against it. When, however, the antibodies are not free in the blood but are attached to the living cells, and when in this position they combine with the antigen, damage results. Theoretically the anaphylactic or allergic state would be one in which there is an insufficiency of free antibodies. The introduction of large quantities of antigen in a sensitized individual results in damage to such a large number of tissue cells due to union with the antigen through the attached antibody that serious or fatal symptoms ensue. If, however, the outcome is not fatal, a large proportion of the attached antibodies will have been neutralized by the first antigen injection. A second injection will then cause little or no reaction.

It appears that damage due to contact of a living cell with antigen stimulates the former to the production of more antibodies. Crude analogies are the tadpole which replaces a destroyed tail with two new ones, or shrubbery which grows more abundantly, with more branches after trimming. Therefore, the antianaphylactic animal or the hyposensitized human being is nonreactive but is actually in the process of producing more antibodies and is therefore still sensitized. If the theory is correct one would not expect desensitization ever to be permanent. Perennial pollen therapy was suggested with the idea that it would eventually desensitize completely. Antibodies would eventually be exhausted, completely used up. We have employed perennial pollen hyposensitization in a large number of individuals. While it has certain advantages over other methods, I do not feel that one of them is that of permanent desensitization. I have seen persons who after three or four years of perennial treatment have been able to go as long as four or five years without further hyposensitization, but I cannot say that I have seen a single patient who was permanently and completely cured, with negative skin reactions and negative passive transfer.

One objection raised against the acceptance of a basic identity between clinical allergy and experimental anaphylaxis has been the observation that after clinical hyposensitization the reactive bodies still appear free in the circulating blood. This, however, as Zinsser remarks, does not preclude the possibility that sessile antibodies have been neutralized. Indeed, one may expect, as a reaction following neutralization, a resulting superabundance of free antibodies or reagins in the blood. While the side-chain theory enables one to visualize a possible type of response, one should not consider that it is the proved explanation. For example, Morris (1936) concludes from his investigation that

“antianaphylaxis is a state of refractoriness which is due neither to excess of circulating antibody nor to antibody depletion, but is the result of secondary changes the nature of which is still not definitely established.”

The fact that desensitization reduces the reactive capacity of the individual presents strong analogy to experimental anaphylaxis and forms another link connecting the laboratory phenomenon with the clinical.

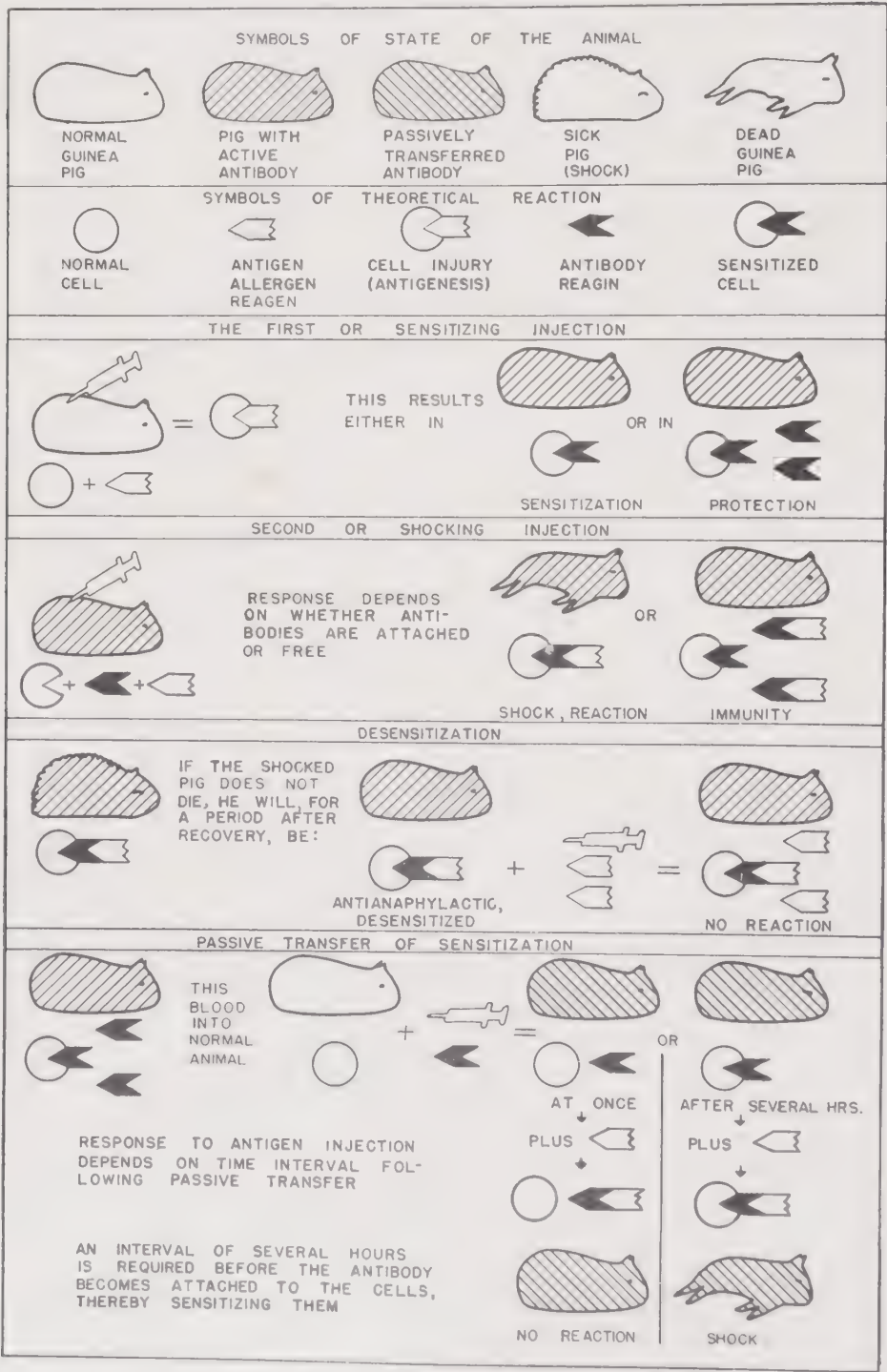


Fig. 5.—Graphic representation of the phenomena of anaphylaxis in terms of the antibody concept. (Acknowledgment to Topley and Wilson, "The Principles of Bacteriology and Immunity," Baltimore, William Wood & Company, for the concept of guinea pig symbols.)

Passive sensitization.—Nicolle (1907) observed that if the blood of a rabbit sensitized to horse serum was introduced into a nonsensitized rabbit, the latter became sensitized to horse serum. Here was a passive transfer of the anaphylactic state. This opened an important field, since studies of passively sensitized animals have established in great measure the fact that sensitization is cellular rather than humoral.

This phenomenon has its clinical analogue, first described by Ramirez in the transfusion of a patient with pernicious anemia from a donor sensitized to horse serum. Subsequently the recipient, driving behind horses, for the first time developed asthma. Frugoni injected serum from an asthmatic, allergic to rabbit hair, into a child. The following day the child experienced an attack of rhinitis following contact with rabbits. While this phenomenon of massive passive transfer has not been observed often, several cases have been reported.

We find another analogy in the well-known Prausnitz-Küstner reaction, in which serum from a sensitized individual is introduced into the skin of a nonallergic, thereby rendering a small area in the region of the inoculation allergic to the particular allergen. Here again there appears to be a short period necessary for fixation of antibody or reagin. This passive sensitization usually persists for three or four weeks.

The Arthus phenomenon. Arthus (1903) observed that if horse serum is repeatedly injected subcutaneously into rabbits, an explosive anaphylactic reaction does not occur, but an edema appears at the site of the later injections with infiltration which may progress to abscess and even gangrene. For a time this was puzzling, since a similar phenomenon could not be produced in other animals. However, this was soon shown to be due to certain differences between the animals.

Guinea pigs are much more susceptible to the production of acute anaphylaxis than are rabbits. Rabbits have a much higher concentration of antibodies in the blood. This suggests that the preponderance of antibodies in guinea pigs is in or upon the cells themselves. The abundance of circulating precipitin or antibody in rabbits in great measure protects these latter against acute shock.

The Arthus phenomenon demonstrated the possibility of chronic or prolonged manifestations associated with allergy. As the writer pointed out in 1924, this gives some experimental basis to the inclusion of such chronic allergies as eczema. As a matter of fact *typical* examples of the Arthus phenomenon are rarely observed in clinical medicine. Probably the commonest is that seen in the course of rabies immunization in which after several injections local infiltration sometimes occurs around the sites of inoculation.

Ross' case (1934) might well be an example of the Arthus phenomenon. A young child who a year previously had received diphtheria toxin-antitoxin, had a scalp injury for which tetanus antitoxin was given. Three days later he developed symptoms which may have been due to serum sickness but so closely resembled those of scarlet fever that the attending physician gave him an intragluteal injection of scarlet fever streptococcus antitoxin.

Although the rash cleared up in a few hours the injection site became indurated and erythematous. Within six days the skin and subcutaneous tissues of the entire thigh, hip and abdomen were involved in a huge necrotic sloughing mass.

Although a few other similar cases have been reported, physicians rarely have occasion to administer horse serum just when a patient is suffering from serum sickness. I have been told of one case which may rest upon a similar

basis. A man convalescing from typhoid fever was given an injection of typhoid vaccine. This was followed in a few hours by tremendous edema of the entire arm which lasted for several days but did not progress to necrosis.

Abell and Schenk (1938) have studied the living blood vessels and capillaries in rabbit ears, finding that local contact with an allergen to which the animal was sensitized (horse serum) was followed by slowing of the blood stream, accumulation of leukocytes in the capillaries where they adhered to the wall, sometimes forming such large clumps as to produce minute emboli. This may well explain the blood leukopenia which accompanies the allergic reaction. With long-continued local contact, thrombosis and necrosis occurred, microscopically resembling the picture seen in the Arthus phenomenon.

Bacterial allergy.—Rosenau and Anderson (1907) produced anaphylactic reaction with extracts from colon, tubercle, anthrax and typhoid bacilli. Subsequent investigations by a number of authors have shown that sensitization to bacteria is a true anaphylactic phenomenon. The work of Avery and his associates (1923) demonstrating a specific pneumococcus polysaccharide and the part which it plays in the specificity of the anaphylactic reaction, places this bacterium and probably the others in the hapten group of antigens.

The tuberculin reaction, a delayed positive skin reaction, was described by Robert Koch in 1882. This appears to rest on a somewhat different basis from that of simple sensitization to bacterial protein, since Baldwin in 1910 showed that infection is a necessary prerequisite to its development. There is evidence that it is associated with sensitization to decomposition products arising from the focal inflammatory areas.

Animals can be sensitized to bacterial vaccines. Attempts to apply this in the clinical allergies, with the demonstration of clear cut prompt skin reactions similar to those seen with pollen, have not been altogether successful.

By analogy one would not expect to obtain promptly positive skin reactions to bacteria which are growing within the body, to which one is constantly exposed. One would expect a rather delayed or "Arthus type" of phenomenon. The positive reactions to bacterial substance used in allergic diagnosis are usually of the delayed type. To me, the picture is clearer if we consider the tuberculin reaction as analogous to the Arthus phenomenon. With this concept, we would assume an identity in the basic mechanism of the prompt experimental anaphylactic reaction to bacteria, and the tuberculin type. An animal not infected with tuberculosis would be more likely to give a prompt anaphylactic response than one which is constantly being hyposensitized to the germ substance.

One possible trouble in reproducing clear-cut evidence of bacterial allergy in man lies in the difficulty in preparing unchanged antigen. In experiments on animals we inject a vaccine. The same material is used for reinjection. When it comes to the study of man we obtain cultures, grow them artificially, kill them by heat or chemicals, prepare the completed vaccine and use this for testing. Obviously this is not the same substance that was originally removed from its source in man. If we could produce a test material which is absolutely identical with the original, the results might be different. The recently developed method of sterilizing vaccines by grinding in a ball mill until each bacterium is broken up, without the use of heat or chemical preservative, should come nearer to producing the native substance. Even so the vaccine has been grown upon an artificial medium which in all probability has produced some change which might be detected by immunologic methods.

CHAPTER V

DISCUSSION OF OBJECTIONS TO AN ASSUMED IDENTITY BETWEEN EXPERIMENTAL ANAPHYLAXIS AND CLINICAL ALLERGY

In the preceding chapter we have briefly reviewed the more important phases of experimental anaphylaxis which find their counterpart in clinical allergy. They cover a surprisingly wide field of the latter. However, certain objections have been raised against the assumption of an identical basis. The outstanding points are the following:

1. Experimental anaphylaxis has been proved to be an antigen-antibody phenomenon. The presence of antibodies may be demonstrated by precipitin experiments. The predominant evidence would indicate that antibody is either identical with precipitin or occurs in the blood in proportionate quantities, so that the measurement of precipitin may be taken as the measurement of antibody. Antibodies of the precipitin type are not usually seen in the clinical allergies. It is, therefore, argued that clinical allergy is not an antigen-antibody phenomenon.

2. While laboratory animals may be sensitized with ease, it has appeared very difficult, indeed, almost impossible, to sensitize man intentionally.

3. Sensitization in animals is an acquired phenomenon, transmitted from parent to offspring only as a passive state. On the other hand clinical allergy appears to be a clearly demarcated hereditary ailment.

4. While the laboratory phenomenon requires a preliminary or sensitizing exposure and a subsequent or shocking one, it would appear that often in man a first or sensitizing contact cannot be demonstrated and may not have existed. There are allergic persons who appear to have experienced their symptoms on first contact with the allergenic material.

Much additional knowledge has been acquired since Coca, who has made numerous most valuable contributions to clinical allergy, first expressed his conviction that the two phenomena were not based upon a common etiology. The facts which appear to me to negate the arguments *contra* listed above may be summarized as follows.

Antibodies versus reagins. The absence of *antibodies* in the blood of human allergies, at least insofar as our present methods can demonstrate, is granted. That there is some sort of antibody in the blood is demonstrated by the phenomenon of passive transfer by the Prausnitz-Küstner method. The designation *reagin* has been proposed by Coca in recognition of their presence and to emphasize that they are probably different from the antibodies of laboratory animals. In other words, there is something in the blood with which we can produce passive transfer in human beings. It cannot be identified by precipitin tests nor by complement fixation reactions.

Doerr and Russ found that the ability of serum to transfer anaphylaxis passively is proportionate to its precipitin content. However, as stated by Seegal, it is sometimes possible to transfer sensitization with serum in which no precipitin can be demonstrated. It may, therefore, be that the antibody responsible for the transfer of anaphylaxis is not a precipitin, but some substance which usually increases in amount in the serum of immunized animals coinci-

dentially with the precipitin. Matsumoto has observed that in guinea pigs precipitins may persist in organs and tissues long after they have completely disappeared from the blood. According to the prevailing hypothesis of anaphylaxis, the reaction is cellular rather than humoral, and the presence of tissue antibodies is therefore of much greater importance than that of antibodies in the blood serum. Until recently the demonstration of tissue antibodies has been difficult or impossible. Khorazo, however, has recently prepared practically pure tissue juice by breaking up the individual cells under high pressure. Seegal and Seegal have demonstrated cytoplasmic antibodies in such tissues. They found, further, that typhoid agglutinin existed in the tissues in from two to four times its concentration in the blood. Occasionally they even demonstrated agglutinins in the tissues when none at all were demonstrable in the blood.

Zinsser gives a number of reasons for considering the existence or nonexistence of antibodies an unimportant part of the discussion.

"It must be remembered that both anaphylaxis and the human *atopies* or *idiosyncrasies* are cellular reactions, the circulating anti-substances being merely expressions of the cellular condition and not necessarily present in the serum at all times. It is a well-known fact that even in true anaphylaxis an animal may be highly sensitive without containing demonstrable antibodies in its blood. Indeed, in the early days of anaphylactic investigation most observers failed to find antibodies in the serum of sensitized guinea pigs, although this serum was often capable of passive transmission; and only isolated observers such as Nicolle and Abt at first found evidences of the presence of antibodies by the delicate measure of complement fixation.

"In regard to the failure of precipitation when reagin is added to its antigen this argument does not carry much weight, since we know that in order to precipitate there must be a reasonably high concentration of antibodies in a serum, much higher than is necessary for anaphylactic sensitization, for instance. Also, we know from the recent development of toxin-antitoxin precipitations that the chemical and physical nature of the antigen may offer difficulties of obtaining the visible precipitate (which is purely a secondary colloidal phenomenon), except under special conditions involving modified temperatures, etc.

"It is quite apparent, therefore, that although we cannot at the present time identify reagins with the well-known antibodies, yet there are many points of close similarity and they must be regarded as specific reaction bodies to a sensitizing antigenic substance, and in this sense the 'atopies' in which a known antigen is involved must be regarded as dependent upon an immunological mechanism, which it is wise for purposes of clearness to classify separately, but which in principle is not fundamentally different from anaphylaxis, except insofar as the anaphylactic responses of man are characteristic and different from those of other species, as are those of guinea pigs, rabbits, dogs, etc."

Harrison (1934) and Caulfield et al. (1937) sensitized monkeys and guinea pigs with pollen extract to which potassium alum had been added. They find that serum from such sensitized pigs contains sensitizing antibodies (reagins) which appear to be identical with those present in the serum of man. Guinea pig serum introduced into human skin with the Prausnitz-Küstner technic caused an identical type of passive sensitization. The antibody responded to manipulation as does human antibody, being neutralized in the antibody absorption test. Serum mixed with ragweed antigen and subsequently transferred no longer sensitized skin sites. Pollen sensitization in the rhesus monkey resembled natural sensitization in man in that (1) the skin of both can be passively sensitized by sera of sensitized animals or man; (2) the skin of both gives positive reactions during active or spontaneous sensitization; (3) the sera of both contain skin sensitizing antibody.

The transmission of allergy.—Symptoms on first exposure.—Although the early work on the transmission of anaphylaxis from parent to offspring which was done with guinea pigs indicated that only passive sensitization was transmitted, a state which was lost by the offspring after the lapse of a month or more, the more recent work which has been carried through, especially by Ratner and his associates, explains the apparent difference between the phenomena in guinea

pigs and human beings. The key to the situation is to be found in the structure of the placenta. There are four main types of placenta in which one, two, three or four cell partitions separate maternal and fetal blood. The placenta of pigs has four separating layers, that of the ruminants three, while man and the rodents have only one layer of cells separating the two circulations. It would appear that the thicker-layered placentas allow passage of antibodies but not of antigens, while the single-layered placenta allows passage both of antibodies and of antigen, thereby permitting active as well as passive sensitization.



Fig. 6.—Pioneers in clinical allergy. *Leonard Noon and John Freeman*, of London, in 1911 first reported successful desensitization in pollinosis, using the principles of allergy.

Ratner presented indirect proof of the transmission of active sensitization in his study of families in which the expectant mother overindulged in certain foods, such as chocolate, and in which the offspring experienced allergic symptoms definitely on first contact with that particular substance. This would suggest an active sensitization in utero.

Bell and Eriksson were unable to demonstrate the direct transmission of allergy from mother to offspring. They studied allergic mothers with positive skin reactions. They obtained blood from the umbilical cords of newborn babies before they had been put to the breast. The skin of the recipient was passively sensitized with the infant's blood. These test sites were then inoculated with those allergens to which the mother had been proved allergic by passive transfer. In no case did they demonstrate transfer of sensitiveness from mother to offspring. The same was true of blood obtained from the infants several days later, after they had been put to the breast. Within the limits of the experiment we may say that although the mother's blood contained reagins, the infant's blood did not contain reagins to the same substances.

The work of Donnally demonstrating the passage of foreign food proteins through the mother's body and milk, into the intestinal tract of the nursing infant, demonstrates another way in which one could be made allergic, later *appearing* to manifest symptoms on first contact.

Finally there can be no doubt that man can be actively sensitized through an intact intestinal tract, through the respiratory tract or even through the skin. In such cases, however, it is not usual for the allergic symptom to appear to come on first exposure. Usually there is a history of previous exposure, or prolonged exposure.

The predominant evidence today indicates that inheritance plays a very definite role in the allergic predisposition. However, there is evidence that this may also be true for animals. Not all laboratory specimens are sensitized with equal ease, even among the animals of the same species. The manufacturers of antitoxins know this, for their experience is that all horses are not equally suitable for antitoxin production. So far as I know no studies have been made through several generations of laboratory animals to determine the inheritance of ease of sensitization.

The difficulty of experimentally sensitizing humans. When Coca expressed his opinion of a fundamental difference between the laboratory and clinical phenomena, from the available evidence the conclusion was practically mandatory that animals could be sensitized with ease, human beings only with greatest difficulty. There was one exception at that time, sensitization to horse serum. Coca did not accept serum sickness in the general class of clinical allergy.

Investigators found no difficulty in sensitizing guinea pigs to horse serum or egg albumin or rabbits to dog serum, but one could not sensitize man to pollen extract or to orris root. Although a few cases of anaphylactic reaction have been reported following the therapeutic use of milk injections, when one considers how many human beings must have been injected with milk during the heyday of the popularity of this procedure, one must agree that it is difficult to sensitize man to cow's milk.

However, as investigations proceeded it became obvious that there are allergens to which animals cannot be easily sensitized and there are others to which man may be sensitized with great ease. Wells and Osborne (1911) found that continuous feeding of a vegetable protein to guinea pigs rendered them immune to this protein so that they were unable to sensitize them to it. Wells found that young guinea pigs bred from mothers fed on oats could be shown to be highly sensitized to oats, when this food was eliminated from their diet. If they continued to feed on oats they acquired immunity thereto. This suggests the possibility that continued contact with a protein or other allergenic substance may tend to produce a desensitization or else interferes with the development of active sensitization.

We have said that man was not made allergic to pollen extract. It was similarly shown that it was difficult to sensitize animals to pollen extract. This is a substance in the natural environment of man or animal with which contact is prolonged. The same is true with regard to milk mentioned above.

These observations formed the basis for the suggestion made by the writer that man or animal may become sensitized with relative ease to a substance with which he comes into only occasional contact, while, with certain exceptions to be outlined, it is difficult to sensitize him to substances which appear frequently in his internal environment.

We were fortunate that the earliest observations leading to the study of anaphylaxis were made following the injection of horse serum into guinea pigs or sea anemone extract into dogs. Studies were continued with egg albumin. These were substances with which the animals came into little, if any, contact. If the original work on guinea pigs had been done with lettuce, carrots or some other constituent of their diet, the observations would have been far different.

The same should hold for man. There should be difficulty in sensitizing him to articles which occur normally and regularly in his diet. It is true that frankly allergic persons are predisposed to sensitization to such articles as wheat, egg and milk, but they are the highly allergic and represent those in whom there has been a rather complete breakdown of the allergy-resisting mechanism. Leaving this group aside, the hypothesis holds.

Let us take by contrast a substance with which man does not usually come in contact, namely, horse serum. Anaphylaxis due to horse serum as contained in diphtheria antitoxin was one of the earliest manifestations of allergy in man, resulting from parenteral injections. The majority of persons who receive therapeutic horse serum develop serum sickness, thus evidencing sensitization. A serum which contains toxin in addition to the antitoxin is even more prone to produce human sensitization than is normal horse serum. Hooker found that 62 of 96 persons who had previously received toxin-antitoxin gave positive skin reactions to horse serum. Gordon and Creswell found that 74 per cent of individuals receiving serum, who had previously received toxin-antitoxin, gave reactions to the serum injections. Tuft found that 28 per cent of children receiving diphtheria toxin-antitoxin became allergic to horse serum.

Jones and Mote found no difficulty in sensitizing humans to rabbit serum. Simon and Rackemann experienced similar success with guinea pig serum, whether administered through the skin or applied to the nasal mucosa.

These evidences of induced human sensitization are to be contrasted with the observations of Brunner, who found that he could not easily sensitize individuals to pollen extract or to orris root even after repeated injections. On the other hand he sensitized to ascaris extract with no difficulty.

It would appear that the nature of the antigen or allergen plays a part. The average person or animal may be sensitized more easily to a foreign protein or substance with which he establishes only occasional contact than to one to which the contact is relatively more constant. This fact appears to hold both for man and animals.

The nonantigenic nature of many allergens. Just as early experiments on anaphylactic animals happened to be done with substances which were decidedly foreign to the animals and their environment, also it happened that the most startling manifestations of experimental anaphylaxis were those observed following the use of substances which contained protein. For a long time it appeared as though protein in some form was the only anaphylactogenic substance, so much so, that Victor Vaughan suggested the term protein poisoning for the phenomenon. So conclusive did the evidence appear to be that the antigen must be protein, that all of the early theories were built upon this conception. We became so accustomed to think of this as a protein reaction that any observation suggesting other possible antigens, such as the early observations of Jobling and Petersen that lipoids might be antigenic, was immediately thrown out as being "not in the picture."

This applied to the laboratory investigations of other possible allergens but on the clinical side we were soon forced to recognize that certain of the drugs could produce symptoms which are indistinguishable from allergy due to protein. These, incidentally, were drugs which were not at all related to protein.

The first systematic study of drug idiosyncrasy was that by Jadassohn. Here was a new problem. Here was clinical allergy, apparently due to what was considered a nonallergenic substance. Now, for the first time in the history of allergy the investigative picture was reversed. As I have brought out previ-

ously, laboratory investigation antedated clinical recognition. But when study of clinical allergy had reached the drug idiosyncrasies, clinical recognition antedated laboratory investigation. It was but natural that attempts should be made to reconcile the apparent inconsistencies of drug allergy. The fact that these inconsistencies do appear to have been reconciled, and with those methods which have been employed in the study of experimental anaphylaxis, creates yet another indirect argument for a basic identity between the clinical and the laboratory subjects.

We have seen that Wolff-Eisner first suggested that hay fever might be an anaphylactic phenomenon. It was he also who first presented a possible reconciliation of drug idiosyncrasy with the prevailing concept of protein sensitization. He suggested that the drug after its entrance into the body might form a compound with the body protein or serum protein, thus forming a new substance (drug-protein) which was still protein but acted as a foreign protein.

Iodine compounds had been recognized as frequent causes of drug idiosyncrasy. Obermayer and Pick iodized proteins, obtaining antigens which on animal inoculation, produced antibodies specific for any iodized antigen, but not for the original protein. This field of investigation was continued by Landsteiner, whose investigations through the last twenty years appear to have thoroughly clarified the problem.

Haptens.—Nonprotein substances which may be combined with protein material to form a new antigen are now called haptens. They are also termed *partial antigens*. Haptens, whether they be simple drugs or complex compounds like the specific soluble carbohydrate of the pneumococcus, when combined with protein form a new protein which is specifically antigenic. However, most haptens can also cause reactions in a sensitized animal even in the absence of the combining protein. Haptens cannot produce sensitization, but once sensitization has been produced by the combined hapten-protein, the hapten alone may produce allergic reaction.

Some of the crossed reactions among haptens are interesting. Doerr, for example, described cases of iodoform sensitization in which the persons also reacted to bromoform. The specific hapten then was not the entire molecule of iodoform but the methyl radicle which also occurs in bromoform. One sometimes sees crossed reactions between haptens, in a very limited field. Thus among the quinine derivatives levorotatory alkaloids, such as ethylhydrocupreine and cinchonidine cross reacted while the dextrorotatory isomers, quinidine and cinchonine did not.

Landsteiner and van der Scheer (1936) found striking specificity in artificial compound-antigens containing aliphatic chains. Succinic acid caused specific sensitization which did not include malonic or glutaric acid. These latter differ only in that they contain one less and one more carbon atom respectively.

Much of Landsteiner's work has been with diazonium compounds which are coupled to proteins by a procedure similar to that followed in synthesizing common azo dyes. He has shown (1936) that the antibodies of an animal sensitized to the azo-protein complex will react with the simple chemical so that later exposure to the chemical-protein complex will fail to produce a reaction. This is demonstrated in the precipitation test. Eagle, Smith and Vickers (1936) demonstrated an actual chemical combination between antibody and hapten, confirming the work of Landsteiner. Landsteiner points out that although there is not yet direct evidence for the presence of antibodies in drug allergy, the existence of some sort of antibodies, perhaps in or on the cells, has not been disproved.

Landsteiner and van der Scheer (1938) have established by the Schultz-Dale technic that haptens can cause anaphylactic reaction even though not conjugated with protein. Guinea pigs were sensitized to certain azo dye-protein combinations. Sensitized uterine strips, free of blood were then exposed to the azo dye, free from its protein combination. Typical allergic response resulted.

With the concept of haptens we are still in the position of being able to reconcile clinical allergy with protein anaphylaxis. Now we come to two new groups of allergens, those represented by *rhus toxicodendron* and the tremendous variety of substances, organic and inorganic, which may be responsible for *contact dermatitis*. Here, again, we are dealing with substances which are often nonprotein, but, in contrast to the classical drug idiosyncrasies, substances which do not have an opportunity to penetrate deeply to combine with blood protein, thus forming a new compound. We are dealing instead, with items which cause symptoms merely from contact with the skin. Even here there is no need for a change in interpretation of the response. The reaction is almost always a local one and we must bear in mind that the fundamental basis of anaphylaxis or allergy is that of combination of the antigenic substance with sessile receptors attached to the tissue cells. Here it may well and probably will, eventually, be demonstrated that the combination of allergenic substance (hapten) with the antibody takes place directly in the locality affected on or in the tissue cells.

Landsteiner and Jacobs (1936) sensitized guinea pigs to parachlorobenzoyl chloride by endermal injection, then found that these animals reacted positively to patch tests and, with anaphylactic shock, to intravenous administration. In this way they demonstrated that a single allergenic excitant could produce either contact dermatitis or classical anaphylaxis, thereby strongly indicating a basic identity in the two reactive mechanisms.

Thus, we are able to cover all phases of differences except that of physical allergy. We shall have more to say of this later, in an effort to reconcile physical allergy as well.

Discussion.—We have seen that there are many factors which explain the difference between clinical allergy and experimental anaphylaxis. One of the most important has been the fact that different types of animals react differently. We have seen this in the usual experimental animals such as rabbits, cats, dogs and guinea pigs. Apparent differences in human beings are no greater than are some of the apparent differences between the dog and the guinea pig. Another reason for apparent discrepancies has been the fact that different types of allergens have been used. As mentioned above, the use of a wider variety of allergens has explained this.

Yet another cause for apparent discrepancy is the fact that allergy in human beings tends to be much more localized to certain tissues or organs, less generalized than in experimental animals. This, of course, is a factor of the conditions of the experiment. With animals we have no hesitancy in giving tremendous doses that will produce systemic reactions, not at all comparable to the normal or therapeutic exposures that occur in man. When occasionally through mistake or otherwise, tremendous exposures are given to man, similar systemic explosive manifestations appear, analogous to those in animals. Furthermore, we do have evidence of local reactions in animals, occurring in different animals at different points of election.

The idea that allergy and experimental anaphylaxis are basically the same is held by a number of experimental immunologists. Zinsser, especially, has discussed the subject at great length and has always maintained an identity. Kolmer has expressed himself likewise and the recent treatises on immunology by Gay and his associates and by Sherwood express the same view. Bronfenbrenner has recently presented his reasons for accepting a common basis.

A large number of the writings on *clinical* allergy have, however, expressed the opposite viewpoint. For this reason it has seemed advisable to present the discussion in considerable detail in this chapter. I agree with Zinsser who has very succinctly summarized his viewpoint in the following paragraphs:

“For these reasons and other less decisive arguments discussed in the text, we have no hesitation in expressing the belief that anaphylaxis to proteins in animals, and all the forms of human idiosyncrasy are basically related in mechanism—depending upon a cellular reaction between a whole or partial antigen and a specific sessile antibody or reagin, which has been developed as a result of previous contact or sensitization. We believe that the important differences between the two forms of hypersensitiveness are largely due to physiological differences between animals and man and, to some extent, to the fact that dietetic and other habits of the human race are far more varied and stretch over much longer periods than those of animals. The acquisition of some forms of idiosyncrasy seems to require repeated exposure over more years than compose the lives of most laboratory animals.

“There are still gaps in the chain of complete identification, but there seems to us much safer ground at the present time than there was five years ago, to repeat the statement we made then that the fundamental physiological principles of hypersensitiveness are the same throughout, and were it not for the confusion of nomenclature which this would involve, we would like to speak of Anaphylaxis of Animals and Anaphylaxis of Man, i.e., the idiosyncrasies.”*

*Resistance to Infectious Diseases, The Macmillan Co., New York, 1931

CHAPTER VI

TERMINOLOGY

Up to this point the nomenclature of allergy has been used with the assumption that the reader is well acquainted with the significance of the terms employed. It is desirable to designate the use to which certain terms will be applied, terms which have been used with widely differing significances by various writers. It is regrettable that in the development of this new subject each investigator has suggested interpretations of his own coinage. As a consequence we have many words originally intended to signify essentially the same thing. Some have accepted the terms as originally defined while others have adopted them, but given them different significance. Some confusion has resulted.

Anaphylaxis.—This was the term suggested by Richet to explain the newly observed laboratory phenomenon. In its original designation it was fallacious, since Richet believed that he was dealing with a primarily toxic substance similar to that of the stinging nettle, to which the animal was naturally immune. The first injection removed this protective immunity, thereby rendering the animal susceptible to the naturally poisonous action of the original extract. As a matter of fact, Richet's dogs did not become more susceptible to the urticating substance but developed an entirely new sensitization to the specific tissue protein. There was no destruction of protection in the sense that Richet intended to signify. To this extent the term anaphylaxis (*without protection*) was a misnomer.

However, I would disagree with those writers who insist that it is still a misnomer. If we consider the word in terms of the present-day conception of antigen-antibody immunity, it is altogether appropriate. A state of immunity exists when there is an abundance of free antibodies in the blood. A state of sensitization exists when these antibodies are sessile, attached to the living cells. Free, circulating antibodies afford protection. In anaphylaxis this protection is lacking. There is an absence of protection in anaphylaxis although not in the sense which Richet intended.

In France *anaphylaxie* is still the term used to designate clinical allergy, although *allergie* also appears in the French literature. Elsewhere allergy has in great measure replaced it.

Present significance.—In this volume we shall use the term anaphylaxis in two circumstances.

1. It is well to have available a term with which to designate the experimental research which antedated and postdated recognition of clinical allergy, work which received its first major impetus from the investigations of Richet and his associates. The word suggested by him appears to be still appropriate for the designation of the laboratory investigations in this field and to distinguish between them and the clinical phenomena.

2. The one clinical manifestation which most closely resembles the outstanding feature of experimental anaphylaxis is the occasional *constitutional reaction or allergic shock* which occurs following exposure to an unusually large quantity or overdosage of allergen. It seems appropriate to continue to call this *anaphylactic shock*. It is the one clinical manifestation which is practically indistinguishable from the classical laboratory phenomenon.

Allergy. Introduced in 1906 by Pirquet, this word like anaphylaxis is no longer used with the significance which was first attached to it by its author. The term, proposed by Pirquet, meaning *altered energy, altered activity or altered reactivity*, is merely descriptive and requires the adoption of no single theory. It does no more than express a fact. This is clearly an advantage over anaphylaxis which bound its originator to a theory.

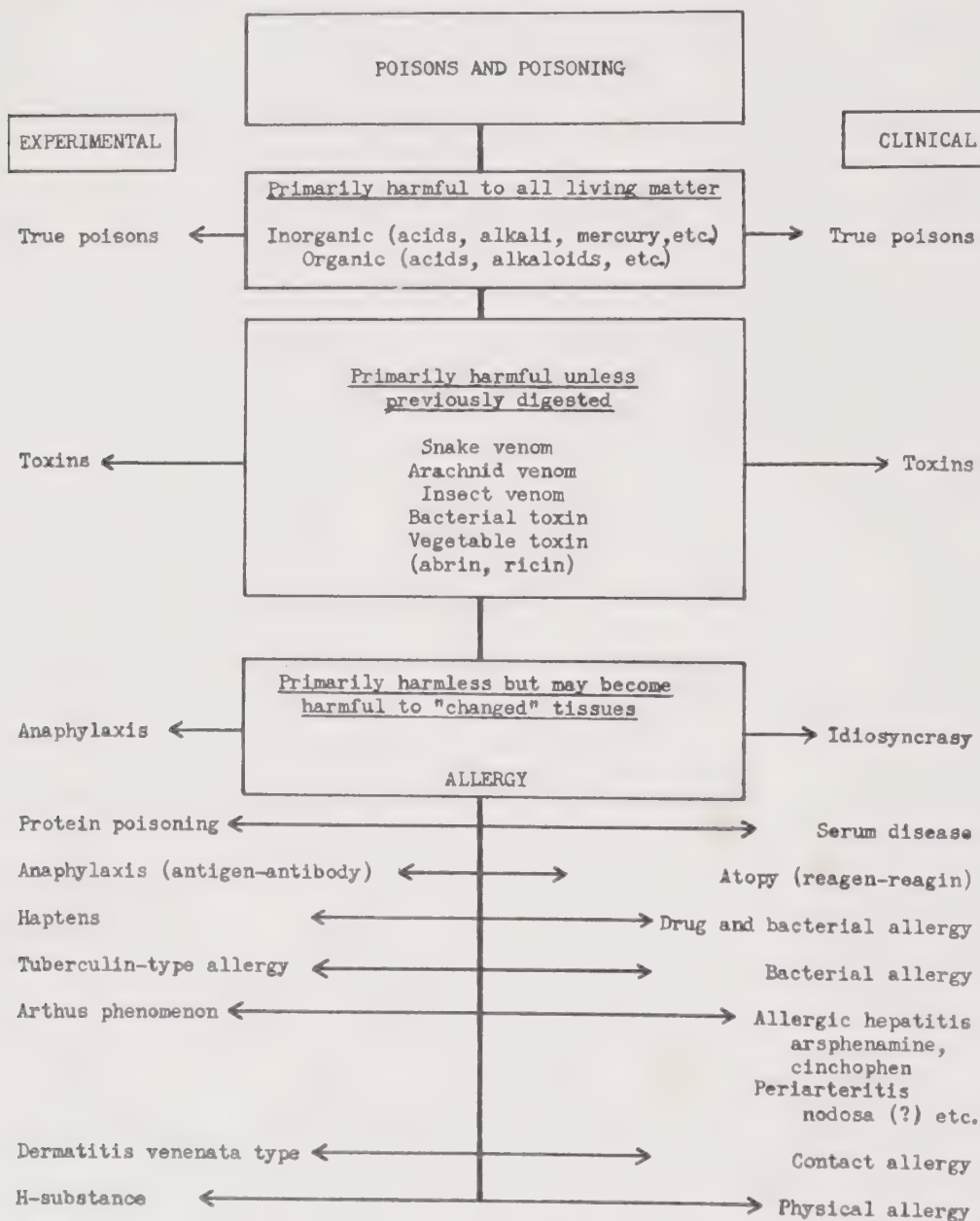


Fig. 7.—The writer's concept of the parallelism between experimental anaphylaxis and related phenomena, and clinical allergy. Like all similar diagrammatic presentations this is not above criticism on certain minor points, but should serve its purpose as a vehicle for general orientation.

Although Pirquet used the term to signify an altered capacity for reaction, in his writings he expressed the belief that an antigen-antibody reaction was the basis of the phenomenon. Doerr extended the originator's definition to include all forms of changed reactivity, irrespective of whether an antigen-antibody reaction could be demonstrated. Coca has given a different inter-

pretation to the term. He classifies as anaphylactic those phenomena in which an antigen-antibody reaction is demonstrated, and as allergic those in which there is no demonstrable antigen-antibody reaction.

Allergy appears to be the most appropriate descriptive term for all of the phenomena which we are discussing, both experimental and clinical. It has several advantages: (1) brevity; (2) it is already in wide use; (3) by its use one avoids the possible confusion that may arise from adapting a term which is used at the same time with other significance. An example of the latter is the term sensitization. There is a growing tendency to apply the term allergy to the clinical phenomena; anaphylaxis to the experimental. I prefer to consider experimental anaphylaxis as a subdivision of the broad subject, allergy. This adds emphasis to the idea that the laboratory phenomena are special manifestations of the same state.

Protein poisoning, proposed by Victor Vaughan, was an appropriate term as long as it appeared that anaphylaxis or allergy could be manifested only against foreign protein. The hapten theory made it still possible to include reactions to nonorganic substances such as arsphenamine, quinine, aspirin, iodine when introduced into the body, as phenomena of protein sensitization or protein poisoning. But if we are to include in the clinical allergies contact dermatitis to such various substances as the heavy metals and synthetic chemicals, protein poisoning is no longer a sufficiently inclusive term, though we might still hypothesize a combining of the foreign substance with the protein of tissue cells.

Atopy.—This term, proposed by Coca to designate what are commonly known as the clinical allergies in which reagin can be demonstrated (see below), commits the user to no special theory. The word merely means "strange disease." Obviously in its interpretation it is even less definitive than *allergy*. If the term allergy is to be used, as recommended by the writer, as a general descriptive term for the entire class of phenomena, it would facilitate discussion to employ some other terms to designate special subdivisions. *Atopy* will be used in this volume, in the sense originally proposed by Coca, to indicate that group of allergic phenomena in which a reagin mechanism can be demonstrated (by passive transfer of sensitization), but *not* in the sense that it indicates a fundamental difference from the other branches of allergy. Atopic eczema can thus be differentiated from contact eczema. Serum disease, classed separately by Coca, becomes atopic in my interpretation. One may even speak of atopic allergy.

Sensitization.—I do not know who first suggested the term sensitization, but I suspect it was borrowed from the terminology of photography where an emulsion of silver salts is acted upon by certain chemicals which sensitize the silver, so that when the latter is subsequently exposed to light it undergoes chemical changes or reaction. The photographic film is sensitized and the material used in the process is spoken of as the sensitizer. By analogy we may speak of the allergen or antigen as being the sensitizing agent. The body is then sensitized to further contact with the same agent. There is some objection to the term, particularly that it is used with a different significance in photography. However, it is fairly appropriate, has come into very general use, and, more important, it provides a verb for the nomenclature of allergy which is not too long and which is not likely to be acoustically confused with other words. It is easier to speak of sensitizing or desensitizing an animal, than of allergizing or anaphylactizing.

Hypersensitiveness.—This is clearly a misnomer and it is to be regretted that it has been used widely. The word is redundant. A person or animal either is sensitive or is not (using this in the significance of sensitized). The prefix hyper is, therefore, unnecessary. *Sensitive* or *sensitiveness* is an unhappy selection since it is used with a different significance, even within the field of medicine. The prefix hyper may be objected to not only because it is redundant but because it expresses only a change of degree or intensity.

Behring and Kitashima, who originally introduced the term hypersensitiveness in 1901, utilized it for another than its present significance. They had found on immunizing an animal to tetanus toxin that it died in convulsions notwithstanding the fact that the blood serum was richly charged with antitoxin. They explained this by assuming the existence of a condition of "hypersensitiveness" to the *toxin*. They were dealing with a primarily poisonous substance to which the animal was naturally *sensitive* and they visualized an increase of this natural sensitiveness, a change in degree or intensity. In its original significance, therefore, the term was entirely appropriate. In Germany where it was originated, it is still the term of choice in the discussions of allergy. The German literature employs the word *Ueberempfindlichkeit*. In Otto's first publications on anaphylaxis (1906) on "Das Theobald Smithsche Phaenomen der Serumueberempfindlichkeit," he adopted Behring's term, although applying it in a different significance. Possibly he was influenced by Richet's notion that the antigen itself must be primarily toxic or by the fact that the phenomenon accompanied diphtheria toxin standardization. Despite its rather wide usage, especially by those who have had much contact with the German literature, the writer feels that the term hypersensitiveness is unnecessary, inappropriate, and would be better avoided.

Antigen-antibody.—An antigen is a substance which when introduced into the body causes or *generates* the production of antibodies. An antibody conversely is a substance which theoretically works *against* the antigen. Combination of serum which contains antibodies with the antigen will under suitable conditions result in the formation of a precipitate. A precursor of the precipitate, present in solution in the blood, is termed *precipitin*. Although there are exceptions as we have seen in the preceding discussion, usually the precipitin content of serum parallels the antibody content. It has therefore become customary to speak of an antigen-antibody combination or reaction as having been demonstrated only when the precipitin reaction is positive. In the terminology of immunity, precipitin corresponds to antibody while precipitinogen corresponds to antigen.

Allergen.—Many or most substances which produce allergic reactions in human beings, when mixed with the serum from the specifically sensitized individual under what presumably should be ideal conditions, fail to cause the formation of a precipitate. This raised doubt as to whether we were dealing with a true antigen-antibody reaction. The probability is that the mechanism is the same with allergens as with antigens, but it seems advisable to retain the two terms as a means of distinguishing two types of allergens, one of which can readily be shown in the laboratory to cause antibodies; while the other does not appear to cause the production of antibodies according to the usual laboratory technique.

Atopen.—This, suggested by Coea and rather widely used in essentially the same significance as allergen, obviously is derived from the word atopy. In accordance with the writer's terminology, allergens may be antigens or atopens.

Reagin.—Although antibodies cannot be demonstrated by precipitin test for the majority of clinical allergens, there is *something* in the blood which *does* react with the allergen. This is demonstrated by the passive transfer phenomenon of Prausnitz and Küstner. If blood from the sensitized person is introduced into the skin of a nonsensitized recipient the latter area becomes locally sensitized toward the particular allergen. This can be proven by subsequent skin testing with the allergen at that point. A positive skin reaction results. Control tests on other portions of the skin, not passively sensitized, remain negative. Obviously something was transferred in the blood. Since it is not characteristically a precipitin, Coca has suggested the term reagin. This seems to be a very desirable term indicating an as yet unidentified and unisolated substance which reacts with the allergen or antigen. Presumably it is the same as antibody but this has not been clearly proved.

Shock organ, shock tissue.—The anaphylactic reaction in different species of animals manifests itself predominantly in different organs or tissues, depending upon the animal. This is likewise and especially true of humans in whom quite a number of different organs or tissues may react. In one person the skin may be the site of reaction, in another the bronchi, and in still another the intestinal tract. Furthermore, the location of the allergic manifestation may vary at different times in the same individual. One allergen may always cause migraine in a certain person while another in the same person always produces diarrhea. Finally one allergen may at different times produce local manifestations in different tissues of the same individual. Doerr introduced the term "shock organ" to indicate the organs or tissues in which the allergic manifestation appeared. The term has come into wide clinical use since its recommendation in clinical allergy by Coca. In hay fever the shock organ or tissue is the mucous membrane of the nose. In urticaria or eczema it is the skin. It may be the heart, the circulatory system or some part of it, the liver (especially in the dog) or some other organ or tissue.

The fact that in one individual certain allergens may always affect one shock tissue while others as consistently affect another, suggests the possibility that sensitization may be a local phenomenon only in certain tissues of the body, equally as well as a general phenomenon. The fact that one person may always react in one shock tissue such as the bronchi while another reacts equally consistently only in the skin, also points in this direction. The specificity of sensitization in shock tissues is illustrated in the experience of one man who in the springtime always developed asthma without hay fever due to grass pollen and in the late summer had ragweed hay fever but no asthma.

Briefly the shock tissue designates the site of the allergic manifestation.

Idiosyncrasy.—This is probably the oldest of all of the terms used to express the general sense of the allergic response. It was in general use long before the phenomena of anaphylaxis were first observed, and employed more especially in connection with the conditions which today we know as drug and food allergy. Its derivation from the Greek fits quite well into the picture. The first portion signifies *one's own, one's particular, one's peculiar*, the second portion, a *mixing together*. Chemically, a mixing together represents a reaction, more loosely a response. Idiosyncrasy may, therefore, be fairly literally translated as *a response or reaction peculiar to the individual*. Interpreted in this way there is surprisingly little difference, literally, between the significance of the word allergy and that of idiosyncrasy.

For this reason the term seems to the author entirely appropriate in discussions of allergy. Undoubtedly the greater part of those clinical reactions which have been designated as food idiosyncrasy are probably allergic.

Hyperergy. This term has been proposed by the writer as indicating an increased sensitiveness or reaction capacity to a foreign substance, for example drugs. There are persons who react much more strongly to the usual dose of atropin or belladonna than do the majority. The person who, with the normal dose, develops an excessively dry mouth, possibly dilatation of the pupils and even, rarely, atropin convulsions, is hyperergic to atropin. He reacts in the normal way but overreacts. A person who after taking atropin reacts with urticaria or vasomotor rhinitis reacts in an altered manner and is allergic.

The person who sunburns extremely easily is hyperergic to the actinic rays. The one who, following similar exposure, reacts with urticaria is allergic. The person who reacts in a normal manner but more easily or more intensely is hyperergic. The term implies increased reactivity. To me this is the logical significance of the term hypersensitiveness and it would be in this sense that I would prefer to use the latter, but since it has been used so widely as a synonym for allergy or anaphylaxis, it would seem more rational to avoid its use altogether, substituting another equally appropriate term.

We may speak of normergy as a normal response to internal or external environmental factors, whether they be food, infection, drugs, chemical or physical factors. Allergy represents an abnormal response to environmental factors.

Summary.—Summarizing this discussion of terminology, we shall use the word *allergy* as a general designation for the phenomena under discussion; *anaphylaxis* in connection with experimental work but more particularly with the reaction phase of experimental work and, in clinical allergy, in connection with shock; *sensitization* as being appropriate in discussion both of experimental and clinical subjects; *atopy* as indicating clinical allergy when reagin participates in the reaction; and *idiosyncrasy* as practically synonymous with allergy but applied more particularly in allergy to foods. It is well not to use the term idiosyncrasy with regard to drugs since, in the past, discussions of drug idiosyncrasy have failed to distinguish between allergy and hyperergy.

PART II

THE GENERAL CHARACTERISTICS OF CLINICAL ALLERGY

Idiosyncrasy is indeed to a large extent nothing but diathesis brought to a point. It is peculiarity of constitution in some one particular feature developed to a height which at first sight seems inexplicable and possibly almost absurd. It is individuality run mad. We must keep in mind that it is by no means always the isolated phenomenon which at first sight it appears. For one man who rises to the height of peculiarity which deserves the name miser, there are a thousand in whom the quality of thriftiness is developed in various degrees beyond what is praiseworthy. The miser is only the thrifty man developed in great excess. So it is with the relations between diathesis and idiosyncrasy; for one person who cannot take the smallest dose of quinine there are thousands who betray unusual susceptibility to the drug and many of them in high degree. Here, I think, we gain an insight into the ways in which idiosyncrasies possibly take their origin. They are diatheses, or parts of diatheses, developed, intensified, and specialized by hereditary transmission.

—JONATHAN HUTCHINSON

CHAPTER VII

THE ALLERGIC DISEASES

The manifestations of allergy are more varied than those of any other disease, due chiefly to the wide distribution of the shock tissues. The earlier diseases were put into this category because of their resemblance to anaphylactic phenomena. Later, maladies such as migraine and gastrointestinal allergy were included chiefly because of association with, or points of resemblance to, the earlier more outspoken allergic diseases. The resemblance appeared in such factors as periodicity; attacks following exposure to specific substances, with relief on avoidance; and the absence of demonstrable organic etiology or pathologic changes. Still more recently diseases have been added to the group because of one or more points in common in the pathologic picture. The local eosinophilia of periarteritis nodosa and the positive skin reaction in tobacco angina serve as examples. Finally some diseases have been placed in this category, not because of any resemblance but because allergy offers the best explanation available at the present time. An example of this is found in agranulocytosis.

Early in the study, diseases were added because of points of resemblance. Nowadays they are added more particularly because of success in finding a normally "nonpathogenic" etiologic factor whose removal results in disappearance of the symptoms and whose reexhibition causes a return.

Cooke's postulates.—At present it is considered hazardous to assign an allergic etiology to a disease manifestation unless the etiologic agent can be proved. Early in the development of clinical allergy Robert A. Cooke formulated a series of postulates to be fulfilled before a substance may be deemed acceptable as an allergic etiologic agent:

1. Sensitization must be demonstrated by one of the following:
 - a. A positive local reaction, cutaneous or ophthalmic.
 - b. The original allergic manifestation must be artificially reproduced at will on introduction of the substance, either inhaled, ingested or subcutaneously injected.
2. It must be shown that the individual has come into contact in some way with the suspected substance in order to permit it to act as an etiologic factor.

These postulates are broadly acceptable, although it should be borne in mind that 1-a often cannot be demonstrated. This is especially true in drug allergy, often also in food allergy. Sometimes inhalant allergens fail to give reactions either on the skin or conjunctiva but do when introduced directly on to the mucous membrane of the nose.

It would be well also to enlarge slightly on 1-b. The words "at will" might be taken to imply that whenever the observer wishes to reproduce the manifestation he must be able to do so. This is not always true. This latter statement holds probably with all allergenic substances, but in my experience, especially so with foods. One may be specifically sensitized to a food and yet have the experience of eating it at times with impunity. This is one of the difficulties in the study of food allergy. As a specific instance, a man is allergic to mushroom as demonstrated by experience (resulting diarrhea) and the presence of a positive skin reaction. Sometimes after eating mushrooms he experiences a sudden diarrhea. At other times he eats them with no resulting ill effect. On the latter occasions he is still allergic and he may even have ingested as large a quantity as, or more than, on other occasions when he has had symptoms. He is, however, temporarily better balanced in his reactive capacity. To describe this condition I have suggested the term *balanced allergic state*, or *allergic equilibrium*.

As another instance, a man experiences attacks of migraine at rare intervals. He never develops his illness except after eating shrimp. But for each time that the ingestion of shrimp is followed by migraine, there are on an average twelve to fifteen times when he eats this seafood with impunity.

This phenomenon sometimes makes the demonstration "at will" difficult.

First Diseases Recognized

The first allergic manifestation recognized as such was that of anaphylactic shock following therapeutic administration of antitoxins and serums. Next in point of time was the description in 1905 by Von Pirquet and Schick of serum disease or serum sickness.

Wolff-Eisner (1906) suggested that hay fever may be an anaphylactic manifestation. In 1911 Noon and Freeman proved the allergic etiology of sea

sonal asthma and hay fever. This was not the first time that pollen treatment had been attempted. We have mentioned the work of Dunbar with pollantin and Weichardt with graminol. Curtis (1900) had attempted the administration of ragweed extract hypodermically, later orally. Scheppegeirell, another American, had applied dried pollen to the nasal mucosa. However, all had been unsuccessful in achieving relief.

The next clinical phenomenon which came under scrutiny as a possible allergic reaction appears to have been drug idiosyncrasy. We have already mentioned the careful studies on the subject by Jadassohn, the suggestion by Wolff-Eisner that sensitization might be playing a part and the extensive laboratory investigations started by Obermeyer and Pick and more especially of Landsteiner, demonstrating that native protein may be chemically combined with other substances such as iodine and azo compounds to form new proteins, against which experimental animals react specifically, while failing to react to the original protein with which the chemical was combined.



Fig. 8.—Pioneer contributors to our knowledge of drug and serum allergy.

Joseph Jadassohn (left), of Zurich, did much early work on dermatitis venenata and inaugurated the patch test.

Alfred Wolff-Eisner, of Berlin, among other contributions, suggested that drug idiosyncrasy may be a manifestation of anaphylaxis. This concept was later verified by Obermeyer and Pick and by Landsteiner.

Schloss in 1912 described cases of food idiosyncrasy in terms of food allergy. The symptomatology in his series included urticaria, angioneurotic edema and eczema. At the same time Laroche, Richet and St. Giron were making similar observations in France.

Just as observation of the bronchial pathology of anaphylaxis in guinea pigs, described by Auer and Lewis, initiated the idea that asthma might be an anaphylactic phenomenon, so the study of serum sickness with its various manifestations suggested other possible anaphylactic or allergic symptoms. In this way urticaria, acute gastrointestinal reactions and subacute joint manifestations came under suspicion.

We have seen that Wolff-Eisner first suggested that hay fever might be allergic, and that drug idiosyncrasy might be explained in terms of anaphylaxis. It was he, also, who suggested in 1907 that urticaria might be due to sensitization to a foreign albumin or similar substance.

Rosenau and Anderson first demonstrated the possibility of sensitization through the intestinal tract. Earliest communications on food idiosyncrasy as a probable allergic phenomenon are said to have been those by Horwitz on egg white and Hutinel on milk in 1908. Doerr was among the first. He quoted the observations of Shofield on a case of egg sensitization. The patient, a boy of 13, experienced urticaria and asthma following ingestion of the smallest quantity of egg. Doerr, himself, was allergic to egg as was Richet.

Doerr's article appeared in 1909. Early communications on the subject of food allergy following this were those of Barbier (allergy to milk, 1910), Castaigne and Gouraud (1910). Schloss, an American, described allergy to egg white, oatmeal and nut and first applied the method of skin testing. The European reports which preceded the work of Schloss dealt with study of sensitization to foods by clinical observation but did not include the newly developing method of skin testing.

Early monograph. One of the earliest monographs, possibly the earliest, on clinical allergy appeared in 1913, by Minet and Leclercq. It is interesting to study this small volume since in it one can find a listing of those clinical diseases which up to that time had been considered possibly anaphylactic or allergic. In it we find twelve pages devoted to serum sickness, nine to gastrointestinal allergy, two to drug idiosyncrasy, two to echinococcus sensitization, and one paragraph each to bronchial asthma, seasonal asthma, cancer and eclampsia. One sentence each is devoted to angioneurotic edema, cyclic vomiting, epilepsy and arthritis. Anaphylactic shock is covered in a page and a half. In spite of the small number of pages devoted to these clinical manifestations, the monograph is 94 pages long, being devoted otherwise to bacterial allergy, medicolegal aspects of anaphylaxis, etc.

Allergy in echinococcus infection as described by Minet and Leclercq is interesting, first, because of its apparently clear-cut anaphylactic nature and second, because this type of infection is becoming rare and we shall probably be seeing it less as time goes on.

Following exploratory puncture of a hydatid cyst or following a spontaneous rupture a sudden acute reaction may occur, almost indistinguishable from acute anaphylactic shock. The patient experiences more or less generalized pruritus with or without urticaria, hyperpyrexia, pallor and sweat, occasionally even convulsions. Rarely there is a sudden death.

The reaction follows the absorption of fluid from the hydatid cyst into the circulation. This same fluid is nontoxic to animals unless they have previously been sensitized to it.

It is especially interesting that during surgical operation under general anesthesia, the spilling of hydatid cyst fluid does not cause reaction. It was shown early in the days of experimental anaphylaxis that animals under general anesthesia (ether) could not be thrown into anaphylactic shock.

Two laboratory findings in echinococcus infection also suggest allergy. (1) eosinophilia, (2) the demonstration of antibodies against the echinococcus antigen.

In recent years the suggestion has been made that intractable asthma may at times be temporarily relieved by subjecting the patient to general anesthesia. This is comparable with the early observations on echinococcus anaphylaxis and experimental anaphylaxis.

The Minet and Leclercq monograph discusses allergy to seafoods, egg, milk, peas, beans, and strawberries. They remark that gastrointestinal allergy is quite rare, *assez rare*. Even as recently as 1923 Richet wrote that allergy to vegetables and fruits (except strawberries) had never been observed.

Development of skin testing.—We come now to the skin test as a special method developed for the recognition of allergic causes. As evolved in routine allergic studies, it is essentially an American contribution. According to Walzer the first test for cutaneous allergy was made by Kirkman in December, 1835. He was, himself, a hay fever sufferer and tested himself to the pollen of sweet vernal grass by sniffing it and rubbing it with his hand. This was scarcely a skin test in the sense that we think of it today. Blackley (1873) reported intentional skin tests, with the application of several types of pollen to the abraded skin, with resultant positive and negative reactions depending upon the pollen used.

Following the discovery of tuberculin, tests were administered *subcutaneously* until the development of the *scarification* method of Pirquet in 1907. In 1909 while studying a case of hypersensitiveness to buckwheat, H. L. Smith applied the Pirquet scarification technic, observing a positive reaction to buckwheat, a negative to a wheat control.

W. L. Moss first employed the intracutaneous test as a preliminary to serum administration. Noon and Freeman (1911) employed the scratch test, but preferred the conjunctival. However, in 1911 Robert A. Cooke in New York first employed intracutaneous testing in general allergic diagnosis. His interest at that time was primarily in inhalant allergy. O. M. Schloss (1912) broadened the field of usefulness of the skin test in applying it to food allergy. He deserves credit for applying the skin test as an available diagnostic measure. Goodale (1914) observed positive skin reactions in horse asthmatics and positive skin and nasal mucous membrane reactions from testing with pollen extracts. Clowes (1913) employed scratch skin tests for the diagnosis of ragweed pollen sensitization. This was in known ragweed cases. Goodale applied it as a diagnostic measure where the etiologic pollen was unknown. Following these observations the scratch method was applied by I. Chandler Walker for the diagnostic recognition of a wide variety of ingestant, inhalant and other allergens.

These early observations, naturally, dealt with the skin test as a helpful procedure. Early interest was in great measure in the *method* of testing. Since then the method has become generally accepted and widely used, and interest has been more in the *information gained* than in the method itself. It provided a new procedure for demonstrating the presence of allergy and for proving an allergic factor in other diseases in which allergy was suspected as playing a part.

In food allergy it soon became obvious that common foods, fruits, vegetables and the like might be allergenic. This was difficult of demonstration prior to the advent of the skin test, when proof of sensitization consisted only in the character of the clinical response.

Diseases Later Recognized

Schloss (1912) called attention to urticaria, angioneurotic edema and eczema as being associated with food idiosyncrasy. Duke (1921) showed that food allergy may be responsible for indigestion and abdominal pain. In 1922 he reported genitourinary symptoms due to allergy. In 1922 Vaughan described mucous colitis associated with food allergy. Pagniez, Vallery-Radot and Nast (1919) suggested allergy as a possible cause of migraine, which was proved experimentally in 1927 by Vaughan.

Allergy has also been found to play a part in the causation of a number of other syndromes, usually of obscure or multiple etiology. At times it is only one of several factors; at others, the chief factor; and yet again not a factor at all. In this group of maladies in which it has been proved that allergy must be considered as a possible factor may be mentioned allergic cough or bronchitis (Colmes, Waldbott), canker sores (Beecher), trichophytosis (Sulzberger), purpura (Alexander and Eyermann), erythema multiforme (Low), epilepsy (Wallis, Nicol and Craig), Ménière's disease (Duke), cyclic or periodic vomiting. Periarthritis nodosa (Kline and Young), Loeffler's syndrome and Tropical Eosinophilia are generally accepted as of allergic origin. Other conditions in which as yet inconclusive evidence of an allergic factor of greater or less importance has been presented include angina associated with tobacco allergy (Harkavy), thromboangiitis associated with tobacco allergy (Sulzberger), status thymicolymphaticus (Waldbott) and essential hypertension.

Physical allergy.—Duke first described urticaria caused by the actinic ray in 1923, by heat and cold in 1924. In 1925 he published his first article describing his concept of physical allergy. A large section of his monograph (1925) is devoted to this subject.

The inclusion of reactions due to physical factors such as heat, light and actinic ray, under the general heading of allergy, completes the revolutionary changes from that period in which it was believed that protein sensitization is an essential concomitant of the allergic reaction. The only apparent justification for including reactions to these physical excitants appears to be (1) in the manifestations of the response which are typically those of allergy, and (2) in the adoption of a broad interpretation of the word. Surely, a person who reacts to sunlight with urticaria reacts in a manner altered from the normal.

Contact allergy.—Here is another manifestation which is now usually considered as allergic, concerning which the same criticisms hold to a degree. That form which was first carefully studied was *rhus dermatitis*, ivy poisoning. Here protein appears not to be playing a part, an oleoresin being the excitant of poison ivy, poison oak, sumac and primrose. The absence of demonstrable protein antigen, the absence of evidence of an antigen-antibody reaction, and the fact that such a large proportion of the population (about 70 per cent) becomes reactive to rhus poison, were facts early put forward as arguments against an allergic interpretation.

On the other hand, the fact that man is not naturally reactive but may be made so experimentally, places rhus contact dermatitis in a category very similar to that of experimental anaphylaxis.

The same is true of other forms of contact allergy, even though they be due to completely inorganic substances such as nickel.

In such cases we are usually dealing with a person who is not primarily sensitized, who after a period of contact becomes reactive, in whom the reaction

is characteristic and usually localized to the area of contact, and for whom there has been developed a special method of testing which has a diagnostic value equal to that of the dermal or endermal test for food and inhalant allergy.

The patch test is not new, being first devised by J. Jadassohn, in 1895. Only in the last few years, however, has it come into wide use as a diagnostic measure, following its popularization in Europe by Bruno Bloch and in this country by Sulzberger and others.

Other diseases.—Although exfoliative dermatitis such as sometimes follows the administration of arsenicals was originally thought to be a manifestation of arsenic poisoning, or poisoning with an arsenic compound, more recent evidence indicates that there is an allergic factor at work. This reaction occurs frequently in individuals who are otherwise allergic and in persons who have received doses of the arsenical preparation which are nontoxic for the average individual.

One altogether different clinical manifestation has been added to the group of the allergic diseases. This is agranulocytosis (granulopenia). The work of Madison and Squier demonstrated that in a predisposed individual amidopyrin can cause disappearance of granulocytes in the blood. Many confirmatory observations have been made. Other drugs such as dinitrophenol, sulfanilamide and novaldin have produced similar changes.

The above are diseases in which allergy may play a dominant role. Not every case of vasomotor rhinitis or urticaria or of the other diseases mentioned is necessarily based upon an allergic response. In some diseases allergy may be one of several etiologic factors, in others it may be the usual etiology, and in still others it may be but a secondary agent, altering or enhancing symptoms. In the last group we might mention rheumatic fever and atrophic or rheumatoid arthritis.

CHAPTER VIII

FUNCTIONAL PATHOLOGY

The pathology of allergy is essentially that of experimental anaphylaxis. We have mentioned Ehrlich's side-chain theory and tacitly accepted it as an explanation for the allergic response, first because it enables one to visualize what *might* be happening, and, second, because it has found such wide favor that much of the terminology of the subject is based thereon. If one accepts the term antibody one accepts temporarily at least, and *faute de mieux*, Ehrlich's conception of immunity as applied to anaphylaxis.

Critique of Side-Chain Theory

Manwaring has presented several reasons why the Ehrlich theory should be accepted only with great reservations. He mentions the skepticism with which immunologic theories have been received by workers in the older medical sciences. Immunology has been described as "an esoteric cult based on an hypothesis that was discarded generations ago by the normal physiologist." Starling describes it as "an ingenuous collection of metaphors." Loeb pays his respects to a "pseudoscience of juggled hypotheses and superficial analyses."

Manwaring's criticism is based on his own more recent studies. He takes up the premises of the side-chain theory in succession.

First major premise of the Ehrlich theory.—There are, either as an integral part of living protoplasmic molecules, or immediately attached to these molecules, highly specialized superficial atomic groups, having selective affinities for extraneous chemical substances. This still remains a theory which has never been exclusively confirmed by experimental research.

Second major hypothesis. The various tissues of the body and corresponding tissues of various animal species differ, either in the number or in the avidity of these specialized atomic groups. This again has not been proved.

Third premise.—The only specific changes in the body during the process of sensitization and immunization are a multiplication of the specific receptors in the tissues and a setting free of a certain number of supernumerary receptors in the body fluids. Manwaring has perfused canine organs with solution containing specific foreign protein with no consequent diminution in the protein titer of the perfusate, thereby indicating that none of the protein was extracted and fixed in the tissues. During the passage the volume of the perfusate did decrease at the same time that an explosive edema appeared in the perfused part. He presents evidence that parenchymatous cells become much more permeable, that intracellular colloids pass outward and suggests that possibly extracellular foreign proteins pass inward. In this process the average parenchymatous cell increases from 50 to 100 per cent in volume. Manwaring adds, although it is difficult to follow his reasoning, that this represents a type of protein absorption that would not reduce the specific protein titer of the extracellular fluid but might allow the specific protein to enter the cell. He concludes that direct experimental study of hypersensitive and immune tissues give no conclusive evidence for or against the hypothetical multiplication and specificity of receptors.

Fourth hypothesis.—The fixed tissues of an immune animal, freed from circulating antibodies, are necessarily hypersensitive, due to an increased number of sessile receptors. Manwaring believes from his studies that immunization and sensitization of tissues are two entirely separate processes. An immunized liver transplanted into a normal dog did not make the recipient anaphylactic. A transplanted anaphylactic liver renders the normal dog allergic.

Fifth hypothesis.—Any specific substance formed or liberated in the blood stream as a result of sensitization or immunization is necessarily an antibody, part of the specific circulating defense of the organism. His conclusions are otherwise. If a sensitized dog is exsanguinated and transfused from an immune donor there is no immediate protection against anaphylactic shock. However, after 24 to 48 hours the animal is completely protected, apparently completely desensitized. According to the Ehrlich theory the circulating immune antibodies should protect it immediately.

Sixth hypothesis.—Circulating antibodies are qualitatively identical in all methods and at all stages of sensitization and immunization with the same antigen. This, also, is contrary to some of Manwaring's recent findings. If a normal dog is transfused from an anaphylactic donor, the former is found to be passively sensitized. If transfused from an immune donor, passive sensitization does not result. In dogs, therefore, there appears to be a qualitative difference between circulating *immune* antibodies and circulating *sensitizing* or anaphylactic antibodies. Since in both types of dogs, sensitized and immunized, the amount of circulating precipitin is the same, Manwaring feels that precipitin in dogs is merely an interesting by-product of sensitization, immunization or toxic injury, with no demonstrable physiological significance. This again controverts the Ehrlich theory.

He has transplanted a normal intestinal loop into a sensitized dog. Such an animal thrown into anaphylactic shock exhibits contraction of the normal transplanted intestine as well as the remainder of the intestinal tract. Explanation: "the contraction of the normal intestine is due to toxic products explosively formed or liberated by the hypersensitive liver." If, on the contrary, an intestinal loop of an immunized dog is transplanted into a sensitized dog, no contraction takes place on subsequent shock. This would indicate that the immunized loop of gut is not only insusceptible to the specific foreign protein but has developed a resistance to toxic products formed and liberated as a result of the anaphylactic reaction in the liver.

Manwaring concludes that it would be well to set aside for future reference the entire schema of immunology based on the specific receptor hypothesis, and to start once again, from the beginning, in an attempt to unravel the mystery of the origin and nature of antibodies. He believes that study of the normal and pathologic permeability of the fixed tissues and wandering cells and the relationship of antigen to enzymes will be instructive.

In discussing Manwaring's conclusions that anaphylaxis and immunity do not rest on a common basis, Topley and Wilson write: "There is no justification for ignoring these interesting and suggestive results, merely because they fail to fit into a mental picture, which seemed to be taking a pleasantly definite shape; but it would be unwise to consign our picture to the limbo of disproved hypotheses, until we are quite sure that these later observations really possess the significance which, at present, seems to attach to them. Apparent

contradictions have a way of resolving themselves into two aspects of a single law, if they are allowed time to find their true position in the general scheme of things."

Evidence which appeared to conflict with the concept of fixed and circulating antibodies and of antibody exhaustion as the mechanism of clinical desensitization was found in the work of Cooke and his associates (1935). Transfusion of blood from "desensitized" ragweed allergic persons relieved the acute symptoms of others, who received no other treatment. This procedure is analogous to passive immunization in the serum treatment of diphtheria and tetanus. Antibody fixation could not be the explanation of protection against ragweed in the donors, since it is obvious that protective antibodies are abundant in the circulation. In such immune blood there was no apparent increase in skin sensitizing antibodies. This suggested a dual mechanism, and Cooke spoke of the antibody in the treated patient as a blocking antibody. These findings were confirmed by Cohen and Nelson, and Reinartz and clinically by Langner and Kern (1938). Loveless (1940) found, too, that this antibody was found only as a result of treatment. It was thermostable in contrast to the skin sensitizing antibody, it showed an affinity *in vitro* for the antigen, and it did not sensitize the skin. This mechanism appears to be that of immunization, and Loveless (1943) reported a correlation between the blocking antibody titer and clinical improvement. Other observers are not in agreement.

Basic Pathology

We know antibodies by what they do, not by what they are. One might say that an antibody is a figment of the imagination, invented to explain certain reactions. Fortunately, when we undertake a discussion of the pathology of allergy we are on surer ground since we are studying reactions which we can actually observe.

Leiomyospasm and capillary hyperpermeability.—The three pathologic responses most characteristic of allergy are (1) smooth muscle spasm, (2) increased capillary permeability with resulting loss of fluid into the tissues, and (3) eosinophilia. Earliest attention was devoted to spasm in the bronchial musculature and in the portal circulation of the dog. Later, spasm of the intestine and the uterus (uterine strip) received attention. Clinically, smooth muscle spasm was referred to as the most outstanding phenomenon.

Later, more attention was given to increased capillary permeability. Today this is recognized as of equal importance to the former. In certain phases of the allergic reaction it appears to be *more* important. Urticaria and angioneurotic edema are examples. The same is probably true of *general* anaphylactic shock. The blood pressure response in shock in rabbits and dogs is, first, one of hypertension to be followed promptly by a most pronounced hypopiesis. This may be interpreted as indicating a preliminary myospastic effect, followed by capillary hyperpermeability. Responses produced by the first phase are soon lost in those of the second.

The loss of fluid from the vascular system in anaphylactic shock is sometimes tremendous and certainly colors the picture to a very remarkable degree. Waldbott believes that the fulminating reaction with pulmonary symptoms, occasionally observed, is not true asthma but pulmonary edema. He feels that edema is the dominant picture. A generalized edema may begin within 15 to 30 seconds following an accidental intravenous injection. This, in his opinion, is the most characteristic feature of human anaphylaxis.

Black and Kemp (1937) have observed increased blood concentration in anaphylactic guinea pigs and in artificially induced hay fever in man. Mayer and Fleisher (1937) found an inconstant increase in blood osmotic pressure in anaphylactic rabbits. These and other observations previously discussed indicate passage of fluid out of the blood, presumably into the tissue spaces. Sodeman and Burch (1937) report greatly increased local subcutaneous tissue pressure following the subcutaneous injection of histamine. Vaughan and Pipes (1938) have observed a similar local increase following endermal histamine injection; accompanying positive skin reactions to test allergens; in spontaneous urticaria wheals; in angioneurotic edema. In all of these, the tissue pressure increase is local, there being no increase in unaffected skin areas. In anaphylactic guinea pigs, on the other hand, Vaughan and Pipes have observed less pronounced but generalized increase in tissue pressure. All of these observations are strongly suggestive of local and general transudation into the tissue spaces.

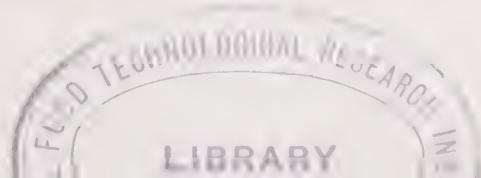
Since it would appear that the capillaries play a great part in the allergic reaction, it is well to understand possible reactions in the capillary system. The average capillaries of the muscles alone have a total area of approximately 6,300 square meters, or more than 3000 times the entire body surface. The capillary wall is so effective a filter that, in the absence of restraining forces, the entire plasma volume could pass from the capillaries into the tissues within ten seconds. If this type of reaction does play a part in anaphylactic shock one may see herein a basis for the suddenness of the reaction. Normally, the movement of fluid through the wall is held in balance by two opposing forces which are usually about equal; capillary blood pressure and the colloid osmotic pressure of the blood. Another factor opposing the passage of fluid through the walls is that of tissue pressure. The vital activity of the capillary wall itself probably also plays a part. It may be damaged, as for example, in anoxemia, with resulting increased permeability.

Eosinophilia.—Eosinophilia appears to be a concomitant of the allergic response. The percentage of eosinophiles in the blood stream varies but it has long been a matter of observation that eosinophilia is often present, particularly in asthma. This appears to be especially true in cases of chronic allergy where symptoms are more or less constant. The eosinophilia, often high, which accompanies some forms of parasitic infection, such as hydatid cyst and trichinosis, probably is associated with sensitization to the foreign protein of the parasites.

The migration of eosinophiles to the site of an allergic reaction is also a fact long recognized. This is seen in the eosinophiles of the asthmatic sputum, in the mucous shreds from cases of colitis, and in the secretion from the allergic nose observed by Eyermann, Hinsel, and others.

If eosinophiles are increased in the blood and in secretions from mucous passages, it is but natural to search for the presence of this type of cell somewhere in the intervening tissues, between the vessels and the mucous surfaces. The occurrence of local tissue eosinophilia at the site of the allergic response is now a matter of general acceptance. Its significance is by no means so clear.

Local tissue response. Kline, Cohen and Rudolph have made interesting studies of the local pathologic response in the allergic urticarial wheal. They produced positive skin reactions in sensitized individuals, then removed portions of the wheals through biopsy, at varying intervals after introduction of



the test substances. They compared these reactions with similar wheals produced by the injection of histamine, a drug which produces wheals in normal nonallergic persons as well as in allergies.

In allergic individuals the allergen produced edema and whealing with an inflammatory reaction of the dermis and subcutaneous tissues, very similar to that of ordinary inflammation. However, at the end of fifteen minutes, 25 per cent of the cells in the local inflammatory leukocytosis were eosinophiles. Within thirty minutes eosinophiles predominated.

Histamine injected into allergic individuals produced a response indistinguishable from the above.

Comparing the histamine reaction in allergies and nonallergies, they found the reaction less pronounced in the latter. In both groups the surface phenomena of urticaria and erythema were similar, but the inflammatory response beneath the epithelium was more pronounced in allergies and was accompanied by a higher eosinophilia.

Mucosal response.—In addition to smooth muscle spasm, increased capillary permeability, and eosinophilia, reactions on mucous surfaces are accompanied by an increased secretion from the mucous glands.

These are the fundamental functional-pathologic changes during the allergic reaction. No matter what the shock tissue the response is very similar, with one or another type of response predominating. The resultant clinical symptoms depend upon the location of the shock organ.

Reversible and irreversible reactions. One difficulty in the pathologic study of allergy has been that the changes are evanescent, disappearing at the termination of the attack. In the allergic reaction there is the possibility of *restitutio ad integram*. Although this is the usual situation in urticaria, migraine and allergic renal colic, there is not always a complete return to normal, as we shall see in bronchial asthma, eczema and colitis. There is the possibility of a return to normal if contact with the offending allergen is removed. It is remarkable what complete recovery may occur without scar tissue formation after an extremely extensive allergic eczema has been cleared up, provided there has been no secondary infection.

After a reaction has persisted for a long time, certain changes occur. If smooth muscle has been spastic for some time, it may gradually undergo hypertrophy. Mucous membranes as in the nose which have been water logged for a long time gradually become polypoid. In these two instances the reaction is not as readily reversible, but, as in eczema, it is surprising what a complete restitution may be accomplished following removal of the exciting cause.

Beyond this, there are some allergic pathologic changes which are completely nonreversible. We have mentioned the Arthus phenomenon in which local tissue edema may go on to necrotization. Periarteritis nodosa is now generally believed to be an irreversible allergic reaction, and pathologists are now willing to believe that there are many tissue reactions which, from the beginning, are probably irreversible, and are allergic in origin.

Tissue alterations include severe degenerative and necrotic changes in all of the coats of the arteries with marked infiltration of the walls and regional tissues with mononuclear cells, eosinophiles and neutrophils, the eosinophiles predominating. Some of the vessels show thrombosis, often with stenosis of the lumen. The veins are not involved. Often voluntary muscle fibers show

degenerative atrophic changes, sometimes with hyalinization and infiltration with mononuclears, eosinophiles and neutrophiles. The picture may involve the coronary vessels. Changes of a similar nature also are seen in the liver and gall bladder.

The preponderance of local eosinophilia with local smooth muscle spasm strongly suggests an allergic etiology, with the arteries functioning as the shock tissue.

It must not be understood that eosinophilia is pathognomonic of an allergic state. Local tissue eosinophilia occurs in other conditions. W. Jadassohn studied the tissue reaction following the local injection of such primary whealing substances as histamine, morphine, pilocarpine, atropine and codeine and found the histologic reaction essentially the same in all, with local eosinophilia. As pointed out by Sulzberger this may well be interpreted as indicating that eosinophiles are not characteristic of an allergic reaction but occur in the presence of any rapid exudative response.

Eosinophilia is a characteristic of the allergic reaction and is often observed in allergic patients. According to Adam, adrenalin does not change the eosinophile count when the latter is normal but does reduce an eosinophilia when present. Atropine does likewise. A cold douche following a warm bath, also fever, diminish an eosinophilia, possibly due to adrenal stimulation.

Theories

Protein poison.—Early in the study of anaphylaxis Victor Vaughan isolated a poisonous substance from every protein with which he attempted the procedure, a poison which produced reactions indistinguishable from anaphylactic shock, but which differed from whole protein in that he was unable to sensitize animals with it as an antigen. This he termed *protein poison*. He considered it as possibly the central nucleus of the protein molecule, identical in all proteins, and the direct cause of anaphylactic shock. The *specificity* of proteins lay not in the central nucleus but in the outlying chemical radicles. The *toxic* or *poisonous* activity lay in the molecular nucleus, identical in all proteins.

With the first or sensitizing injection of a foreign protein, the latter continued to exist as such, unchanged in the body until the tissue cells had learned to elaborate an enzyme which would digest the foreign material. The chemical constitution of the molecular elements surrounding the protein nucleus being different for each protein, a special enzyme specific for that particular protein must be elaborated before the protein can be digested. Obviously, a general proteolytic ferment such as that found in the intestinal tract would not do in the internal structure of the body since this would result in autodigestion. Furthermore, such a general ferment would be unnecessary in the tissues since under normal conditions the foreign protein would have been digested as it passed through the stomach and intestines.

With the gradual elaboration of the specific digestive enzyme (antibody), and resulting digestion of this foreign protein, small amounts of the protein poison are liberated, so gradually as to cause no symptoms. But on the re-injection of the same whole protein, the enzyme now present, pre-formed, digests the foreign protein so rapidly, liberating such large quantities of protein poison in a short time, as to produce the symptoms of anaphylactic shock.

He succeeded in dividing all proteins studied into two fragments, the protein poison, and a nonpoisonous fragment which following injection pro-

duced no symptoms, *but which did sensitize* the animal against reinjection of the whole protein. He, therefore, had a sensitizing fraction and a shocking fraction. Vaughan's enzyme corresponded with Ehrlich's antibodies. Vaughan did not believe that the reaction between foreign protein (antigen) and enzyme occurred, in anaphylaxis, in the blood stream. He accepted the evidence for tissue sensitization rather than humoral, and conceived of the digestion of a foreign protein as being accomplished by the living tissue cells, with the enzyme still attached thereto. In this way the protein poison became most effective.

Although in the early days of the study of anaphylaxis this theory was probably the most popular in the United States, newer phenomena were observed which it did not explain. Together with the other early theories, it is no longer tenable. However, it is of interest to note that one of the most recently proposed theories, that of Manwaring, is an enzyme theory. The chief phenomenon preventing acceptance of Vaughan's theory was the gradually accumulating evidence that the poisonous substance must be formed in the body itself by some reaction, either chemical or colloid, rather than introduced with the antigen. The extremely minute amount of antigenic material which will produce shock as severe as that produced at other times by one hundred or one thousand times as much, strongly suggests that the antigen, instead of providing the poison, provides the stimulus for some type of reaction within the body which results in the formation of the poisonous element from some constituents of the body itself.

Histamine. Meanwhile, studies have proceeded along another line. Histamine (beta-iminazolyethylamine) is derived from histidine (one of the essential amino acids) by decarboxylation. It is regularly produced in the intestine by organisms of the *Escherichia* group. It is present in the tissues generally—even in leucocytes—but how it is formed in the tissues is not known. It has been obtained in crystalline form by Best and his associates.

Histamine stimulates the gastric secretion, dilates the arterioles and capillaries in man, lowers blood pressure, constricts the bronchioles, contracts the "sphincter" of the hepatic veins, dilates the pial vessels, and raises the cerebrospinal pressure. It is an antagonist to epinephrine, and probably acts as a stimulus to its production. It is liberated from the tissues in anaphylactic reactions, and is neutralized by histaminase.

Biedl and Kraus, in 1909, noted the resemblance of anaphylactic shock to peptone shock which Dale and Laidlaw, in 1910, ascribed to histamine. Auer and Lewis called attention to the bronchospasm in anaphylactic reaction in the guinea pig, and ascribed it to histamine. Manwaring found the fall in blood pressure in the anaphylactic animal to be due to the liberation of a depressor substance from the liver. Since then, a number of observers have found histamine in the tissues of the body, especially in the lungs of the guinea pig and in the liver of the dog. Liberation of histamine into the blood plasma was found to occur in the anaphylactic reaction except in the calf and rabbit. Code found the plasma histamine increased two to thirteen times in the shocked guinea pig, and two to eighty times in the dog. Trypsin will release histamine from the tissues, as does antigen in the sensitized animal.

Pure histamine has not been recovered from the blood of the shocked animal because the quantities present are too small, but the substance present in the blood has the characteristics of histamine. It is basic, dialyzable, stable to boiling HCl, inactivated by histaminase, inhibited by arginine, it lowers blood pressure, and produces wheals in human skin.

There are many who are committed to the theory that histamine is liberated in the anaphylactic reaction and does damage to the cells, thereby producing the symptoms of shock. It has been suggested that the antigen-antibody reaction or a proteolytic enzyme may affect the cell by neutralizing an antienzyme, activating an activator, or by changing the pH. This, then, permits the action of an intracellular enzyme which breaks the peptid bond of the amino acid chain and liberates histamine.

Many objections have been raised to this theory. The primary hypercoagulability, the later incoagulability of the blood, the leucopenia, and the hemoconcentration are not explained by the formation of histamine. The discovery that heparin is liberated from the liver cells accounts for the incoagulability of the blood, but does not explain the other blood changes. The failure to find an increase in plasma histamine in the rabbit may be explained by the finding of many mural thrombi in the pulmonary vessels in this animal with the accumulation of leucocytes there and the reaction occurring primarily in the pulmonary vessels. The inability to establish chemically the presence of histamine in the blood leaves the theory still unproven. Dragstedt states that histamine apparently is present at the site of the anaphylactic reaction in quantities sufficient to produce the reaction and that it could explain the different findings in the reaction.

It is generally assumed that the H-substance of Lewis is histamine.

In normal men, not allergic, the amount of histamine in the blood is quite constant; in the allergic individual it is quite labile. Allergic reactions are not constantly associated with increase in the plasma histamine. The only statement that can be made safely about the relationship of histamine to the allergic reaction is that there may be much more fluctuation in the histamine level than is found in the nonallergic person. The recent introduction and use of the antihistaminic drugs has not greatly aided our thinking. These drugs are of great help in relieving the symptoms of pollen hay fever, but do not help so much with the perennial allergic nasal allergies nor with asthma. Since all of these conditions are believed to have a common basic mechanism, there is no adequate explanation for their apparent selective behavior on the assumption that they are antagonists to histamine.

Menkin has isolated a factor in inflammatory exudates which induces increased permeability of the capillary wall. It is not a protein substance but contains amino and carboxyl groups, appearing to belong to the relatively simple polypeptids. He believes it is not histamine nor the H-substance. It has been isolated and crystallized and called leucotaxine.

Discussion.—In this chapter we have reviewed present knowledge of the functional pathology of the allergic response in general. The pathology of the local manifestations of clinical allergy will be discussed under the appropriate headings.

For the present we may state that the histamine theory has many adherents, is an attractive hypothesis and, like Ehrlich's side chain theory, offers an easy way of discussing the various reactions that occur in the anaphylactic animal. Whether it is the correct explanation is still open to argument. Available data would tend to incriminate histamine in the anaphylactic reaction with much more assurance than in the allergic reaction. Further studies should throw more light on the whole subject.

CHAPTER IX

INCIDENCE OF ALLERGY

Until within recent years there has been little statistical evidence concerning the frequency of the allergic diseases. Obviously, as long as a disease is unrecognized there will be no statistics. John Bostock after nine years of study knew of but 28 cases of summer catarrh and another 10 in which the diagnosis was uncertain.

General Estimates

The first systematic effort at statistical compilation was that of Scheppegrell of New Orleans who in 1916 concluded from a questionnaire sent to physicians of Louisiana that about one per cent of the population of the United States suffers from hay fever. Balyeat stated (1930), although he does not give his authority, that about 65 per cent of all hay fever victims finally become asthmatic.

Rackemann (1931) found that in the Industrial Clinic of the Massachusetts General Hospital the incidence of asthma among 2,170 admissions was 5 per thousand or 0.5 per cent. He concluded that a figure of between 0.5 and 1.0 per cent for the incidence of asthma is probably about correct.

Hoffman (1926) concluded from his study of industrial insurance and life insurance statistics that there are about 500,000 cases of asthma per year in the United States or slightly under one case in 200 population. Isserlin (1924) estimates the same number for Germany, his conclusions being reached from records of compulsory insurance. Hoffman further estimated that in the United States there are about 13,000,000 work days lost per year on account of asthma. Klewitz found only 4.8 asthmatics per 10,000 inhabitants in the Province of Ostpreussen. Coke estimated that in England there was one asthmatic in every 500 of the population.

The Draft Board during the World War rejected Americans at the rate of 2.45 per thousand on account of asthma associated with emphysema and bronchitis. Of course this was a selected age group, between 18 and 31, and gives no idea of the incidence of asthma in other age groups. Obviously, also, there were probably many asthmatics accepted as well as rejected. The writer has found from a study of the statistics of the Medical Department of the Army during the World War that in the United States Army between April 1, 1917, and November 31, 1919, 7,445 enlisted men were admitted to hospitals with a diagnosis of asthma. This represented two asthmatics for every one thousand soldiers. This added to the 2.45 per thousand rejected in the draft would give a final figure of approximately 5 per thousand or 0.5 per cent, which corresponds remarkably well to the conclusions reached by Rackemann, and by Hoffman.

The statistics for World War II are not available, but they would probably have little significance. Many men with clinical asthma were accepted for service. Some of these were discharged as unfit for duty, while others were able to carry on more or less normally in military life. Some men concealed their ailment in order to enter service, while some medical examiners accepted men in spite of a history of asthma. The amount of disabling asthma discovered in the military forces is probably a very unsatisfactory index as to the amount, even in that age group.

Since asthma is rarely fatal the mortality rate is of no value in giving us any idea as to the frequency of the disease. Hoffman estimated the mortality in the United States as 20 per million; in England and Wales, 54 per million population.

Population Surveys

As interest in the allergic diseases grew it was but natural that investigators should wish more reliable information concerning the incidence of the disease. More accurate community population surveys were in order. The early surveys paid particular attention to asthma, hay fever and urticaria, those maladies which were considered as proved allergic. As more diseases were added to the list, particularly food idiosyncrasy, migraine and allergic eczema, later surveys would be expected to show higher incidences. This we shall see has been the case.

Spain and Cooke.—The earliest of these modern surveys was that of Spain and Cooke (1924) who in a survey of 506 medical students, nurses and patients concluded that 3.5 per cent of the population are subject to hay fever or asthma at some time in their lives. They estimate the total incidence of human hypersensitiveness as approximately 7 per cent.

Piness and Miller.—The next population survey dealing primarily with asthma and hay fever was that of Piness and Miller (1930) who surveyed two entire communities in the West. In the first town of 3,000 population 4.4 per cent had hay fever while in the second of about 1,000 population, approximately 3 per cent suffered from the disease; 21.6 per cent of the hay fever victims in both cities also had asthma. These were mining communities in the far West.

Rowe.—With the addition of food allergy and its several manifestations to the symptoms searched for in surveys, the percentage incidence grew. Rowe made a survey (1931) of 400 unselected university students and nurses. He found that 43 per cent presented a family history of probable allergy; 35 per cent gave a personal history of probable allergy; 31 per cent suspected foods as possible causes of symptoms.

This survey was entirely comparable to those made by Spain and Cooke, Piness and Miller since in all three the study consisted in interrogatories without objective corroboration by skin testing. However, the discrepancy between 7 per cent and 35 per cent is too great to be explained on geographic or age difference. The addition of food allergy, which was Rowe's special interest at the time, might account for much of the difference, but the question naturally arises whether there was a difference in the selection of criteria for inclusion or exclusion as allergic.

Vaughan.—At this point the writer contributed his survey, in which we may see an explanation for the apparent discrepancy. Vaughan (1934) made a survey of an entire community comprising 508 individuals living in and around the village of Clover, Virginia.

Instead of having a single group of criteria for classification as allergic, two different sets of requirements were adopted. Patients accepted as frankly allergic, designated *major allergies*, included those with (1) typical history of bronchial asthma, (2) recurrent seasonal hay fever, (3) chronic or frequently repeated urticaria, (4) typical history of migraine, (5) history of recurrent gastrointestinal upsets, with one or more of the preceding symptoms *occurring in association*, although not necessarily as outspoken as in (1)

to (4). The evidence for inclusion in group 5 was strengthened when the individual could specify particular foods as responsible for symptoms. (6) There was yet another small group comprising individuals who had or gave history of having had the more chronic forms of dermatitis in which, however, they could name the etiologic agents and had relieved themselves by avoidance thereof.

The second group comprised no cases of typical asthma or seasonal hay fever since these obviously belonged in the first. It did include persons with the symptomatology of vasomotor rhinitis occurring out of season. Such were those who gave a history of sneezing attacks after exposure to cosmetics, house dust, fumes, grains, wheat flour, and those who were in the habit of sneezing half a dozen times each morning on arising, etc. It was surprising to note that most of these persons had, themselves, discovered the offending agent and through its avoidance had relieved themselves of the symptom. They were, therefore, not ill at the time of the survey and only gave a history of having had occasional allergic symptoms in the past, relieved by the avoidance of the recognized cause.

The group also included persons with history of digestive upsets or headaches or urticaria at some time in the past, and due to the eating of some particular item of food. A history of indigestion was not accepted as evidence unless the individual was able to name a potential allergen, usually a food, which he had learned from experience did cause symptoms, and had found from experience that its avoidance had relieved him.

In this group the occurrence of a symptom was not sufficient evidence. The patient must have recognized the offending allergen. As a consequence the members of this second group were for the most part apparently normal individuals giving only a history of evanescent allergic manifestations at some time in the past. This group has been designated *minor allergics*. They had presumably been allergic and many of them still were when exposed to the offending agent. However, they had been able to cure themselves by virtue of the fact that they recognized the cause and that it was an etiologic agent which could be avoided with ease.

In the population survey the writer found 10 per cent frankly allergic. These were the group of major allergies. The second group of minor allergies included 50 per cent of the population. The total incidence of allergy in this population from this anamnestic survey was, therefore, 60 per cent. But for comparison with the previous surveys the 10 per cent figure for frank allergy must be used.

Five and three-tenths per cent of the population had, or gave a history of having had, frank hay fever; 3.3 per cent asthma; 2.9 per cent vasomotor rhinitis; 4.9 per cent urticaria; 4.5 per cent gastrointestinal allergy; 3.1 per cent allergic migraine; 0.6 per cent allergic eczema; and 0.39 per cent angioneurotic edema.

Among the minor allergies food sensitization played the dominant role. Forty-three per cent of the entire population gave some history of food allergy. This is reasonably comparable with Rowe's figure of 31 per cent in a limited age group giving a history of definite allergic disturbances probably due in whole or in part to specific foods.

Since the report of this survey the figure 10 per cent appears to have been quite generally accepted. Bray states that human beings are allergic up to 10 per cent. Seegal puts the incidence of atopy at 10 per cent.

Jimenez.—Although in the next chapters I shall offer an explanation of the surprisingly high incidence of minor allergy, the conclusions reached are so at variance with preceding surveys that they would seem to require corroboration. Jimenez (1934) reported an independent investigation which he had been following in the preceding three years. It was based upon an interrogatory comparable to that of Rowe, filled in each year by freshman students at the Health Service Unit of the University of Michigan. His conclusions were based upon records of 6,935 individuals.

Eleven and nine-tenths per cent gave a history of eczema, rose fever, hay fever, asthma or a combination of these; 22.3 per cent gave history of asthma, gastrointestinal upsets, food idiosyncrasy, frequent colds, headache, etc., and at the same time a good family history of sensitization; 19.2 per cent had had no allergic symptoms but gave a strong family history. Jimenez concludes, "On the basis of the history of nearly 7,000 entering students we conclude that about 35 per cent belong to the class of sensitized persons. On the same basis we find 20 per cent of potential cases which later in life may or may not develop symptoms of sensitization. More than half (54 per cent) of man and women college students should receive a complete sensitization study."

Pipes made a study directly comparable to our own, covering 700 residents of Louisiana. He found 13.6 per cent suffering from major allergy, 35.8 per cent from minor allergy, total approximately 50 per cent; 8 per cent were hay fever victims.

Cohen* states that among the large number of children certified by their attending physicians as free from physical and mental defect and from behavior problems, followed in the work of The Associated Foundations, Western Reserve University, over a number of years, approximately 50 per cent eventually developed some evidence of allergy.

Service (1938) made a survey of a city of 35,000 population to determine the incidence of the more common allergic diseases. One thousand families, totaling over 3,000 individuals, were surveyed. Forty-five per cent of the families had some form of allergic disease; 20 per cent of the total number of persons were allergic. Three per cent of the individuals had asthma, 10 per cent hay fever, 2.6 per cent eczema, 2.7 per cent migraine, 2.6 per cent urticaria and 2.1 per cent gastrointestinal allergy.

Objective Surveys

If 50 per cent or more of the population at large is suffering from major or minor allergy, one would logically expect that objective evidence would also be available; that the history of past allergic symptoms could be confirmed by positive skin reaction. No large number of investigations have been reported on the skin testing of apparently normal persons, but those that have been made lend confirmatory evidence in great measure. Harkavy, using only four allergens, tobacco, ragweed, timothy, and horse dander, found positive skin reactions in 38 per cent of a group of 200 general medical ward patients. Rackemann and Simon, using 8 test allergens, ragweed, horse serum, wheat, "silk floss," cat hair, feathers, timothy and orris powder, found positive reactions in 50 per cent of 60 presumably nonallergic persons.

Summary.—I believe that we shall eventually find ourselves within striking distance of the actual facts when we accept the statement that approx-

*Cohen, Milton B., Cleveland, Ohio. Personal communication.

imately 10 per cent of the population suffers from frank allergy, major allergy, while an additional 40 or 50 per cent have experienced, or will experience, some minor evanescent allergic manifestation, not sufficiently pronounced to require medical consultation. A qualifying statement should be that these surveys have been made for small sections and do not necessarily apply to the country as a whole, since geographic, climatic, botanical and other factors play parts of varying importance in different sections.

Sex Distribution

Bray writes, "The relative incidence of males to females varies with the different manifestations and even with the same manifestation at different ages. In general, I find that eczema is more common in males than females, migraine in females than males, whilst hay fever is of equal occurrence. Asthma is twice as common in boys as in girls, slightly more prevalent in females than males from the age of puberty to the menopause, after which it is slightly more frequent in males. In fact, practically all allergic conditions are more common in males than in females from birth to fifteen years, and in females than in males from the ages of fifteen to forty-five years."

He believes that puberty is a decisive milestone toward which a great number of males will improve and beyond which a greater number of females develop symptoms. It is not unusual to obtain a history in a male of having had asthma until he left school or commenced work, and in a female of having started with her trouble after her school years or after her marriage. Women who commence to have asthma at puberty or after marriage and whose attacks are related to menstruation are often relieved following the menopause.

Coke, Rackemann and Walker believe that asthma is about equally divided between the sexes. Jaeger and Goldschmidt found a higher incidence among females while Salter found a preponderance among males. Kammerer, Adam, Klewitz, Piness, Berkart, Rackemann and Coke variously found from 53 to 57 per cent of their series male. Hoffman found that among deaths from asthma in the United States 55.3 per cent were among males.

Nelson, in a study of the age-sex incidence in 1,786 allergic individuals, finds that males predominate in a proportion of two to one in the first decade of life. With the onset of puberty the proportion is reversed and females predominate in the ratio of five to three. The greatest period of increase is in the second decade, during the years of physiologic adjustment in the female. From the middle of the third decade on, the sex incidence is fairly equal; 39.11 per cent of hay fever patients were found to also have asthma.

The average of most investigators gives about 55 per cent male distribution, 45 per cent female, in asthma. Hausel finds in his cases of nasal allergy 54.3 per cent female, 45.7 per cent male.

Many extraneous factors influence the admission rate by sex to a medical clinic. To obviate this, in my community survey, I have compared a sex distribution in the group of frank allergies with that in the population at large, after having first excluded the minor allergies. Feeling that the incidence among minor allergies might complicate the issue in comparing the findings with those of previous investigators quoted above, the study has, therefore, been made upon a community group consisting of frankly allergic individuals and clearly non-allergies. Persons in whom the age was not specified were also excluded.

This selected community comprised 223 persons, of whom 103 were females, 120 males; 46.2 per cent of the population, therefore, were female; 44.2 per

cent of the *nonallergic moiety* of the population were female, while 53.1 per cent of the *allergic population* were female; 46.9 per cent of the allergies at all ages were male, 53.1 per cent female.

There were 120 males in the population, of whom 23 or 19.1 per cent were clearly allergic. There were 103 females of whom 26 or 25.2 per cent were clearly allergic. These figures are obviously larger than the 10 per cent incidence of allergy discussed in the last section, because of the fact that the minor allergies have been removed from consideration.

These figures would indicate that in a given population with equal sex distribution, for every four allergic males there would be five allergic females. This does not include minor allergy.

TABLE I. SEX DISTRIBUTION OF ALLERGY IN A COMMUNITY SURVEY

	MAJOR ALLERGY	MINOR ALLERGY	NO ALLERGY	TOTAL
Male	23	118	97	238
Female	26	143	77	246

53.0% of major allergic population are female

44.2% of nonallergic population are female

58.4% of males are allergic (major and minor)

68.0% of females are allergic (major and minor)

When we study the minor allergies in this series we reach the same conclusion. There are 118 males with minor allergy, 97 males without allergy, making a total male population of 215. There were 143 females with minor allergy and 77 females without allergy, making a total female population of 220. Fifty-five per cent of the males had minor allergy, 57.2 per cent of the females.

Age Distribution

Asthma.—The frankly allergic individual usually develops some symptoms within the first decade of his life. Indeed, those who have made a special study of the age of onset of asthma, from the time of Hyde Salter (1860) down to the recent study of Rackemann (1927) agree that between 29 and 41 per cent of asthmatics date the onset from the first decade. About one-third of all asthmas begin before age ten. It rarely has its onset before six months, but usually before six years. I have seen a case of asthma in a child not three hours old.

Hansel states that among 420 cases of nasal allergy some of whom had asthma, the onset occurred within the first decade in 54 per cent.

According to Walzer onset after the first decade, during the second, third and fourth is distributed about equally among these latter. Forty-five to 55 per cent of cases experience the onset in the second to fourth decades. Only 12 to 18 per cent have onset in the fifth or sixth decade, and a very small percentage after age fifty or sixty.

Bray finds in a series of 4,317 asthmatics that 33.7 per cent experienced onset during the first decade, 14.1 per cent in the second, 17.5 per cent in the third, 16.3 per cent in the fourth, 10.5 per cent in the fifth, 5.7 per cent in the sixth and only 2.2 per cent after age sixty.

Among 1,390 whose asthma started during the first decade, 22.25 per cent developed it in the first year, 17 per cent in the second, 13.5 per cent in the third, 10.75 per cent in the fourth, 10.25 per cent in the fifth, 8.5 per cent in the sixth, 6.25 per cent in the seventh, 5.5 per cent in the eighth, 4.25 in the ninth

and 1.75 in the tenth. It becomes obvious that of those who develop asthma during the first ten years of life, almost 85 per cent have done so by the sixth year.

There is little doubt of an hereditary predisposing factor which will determine in great measure the age of onset of symptoms, not only in asthma but in other forms of allergy. The heavier the allergic inheritance, the earlier manifestations are likely to appear.

Spain and Cooke found that 79.1 per cent of asthmatics with *bilateral inheritance* first manifested symptoms during the first decade. Cooke and Vander Veer found 66.2 per cent, Balyeat 58.6 per cent. According to Spain and Cooke 36.3 per cent with *unilateral inheritance* develop symptoms during the first decade. Cooke and Vander Veer found 32 per cent, Balyeat 32.3 per cent. Among those asthmatics with *no evidence of inheritance* Spain and Cooke found that 21.7 per cent developed symptoms in the first decade; Cooke and Vander Veer 17.7 per cent.

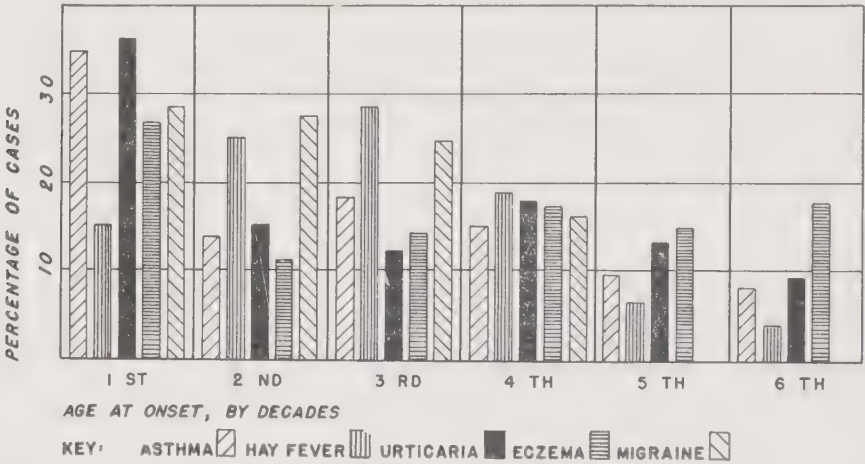


Fig. 9.—Age of first appearance of allergic symptoms, by decades. While this varies with different symptoms, roughly one-third of major allergies develop some evidence thereof before the age of 10 years, two-thirds before 30 years of age. The percentages shown in the chart are those recorded by Bray, "Recent Advances in Allergy," Philadelphia, 1934, P. Blakiston's Son & Co.

Migraine.—Not much has been written concerning the other allergic manifestations. The early onset of infantile eczema is familiar to all. Migraine is usually considered a disease of adults, but my series shows an early onset, with approximately one-third affected in the first decade, two-thirds by the second, and nearly all before age 30. Table II includes comparison with similar conclusions reached by others.

TABLE II. AGE OF ONSET OF MIGRAINE
(IN PER CENT)

	VAUGHAN	McCLURE AND HUNTSINGER	SHELDON AND RANDOLPH	ANDRESEN
Before 10	49.3	{ 83 } 95	39.4	7
11-20	16.4		33.0	48
21-30	25.3		18.9	25
31-40	3.0		7.1	14
41-50	4.5		0.8	{ 6
After 50	1.5		0.8	

It will be seen from the above table, representing 4 series of investigations, that migraine usually commences before age 20 and that about 90 per cent of cases have onset before age 30. Indeed, a high proportion commence in early childhood.

Gastrointestinal.—Clein reports (1938) that 78 per cent of a group of 100 allergic children showed some evidence of allergy before they were 4 months old. The three main infantile allergic symptoms were eczema, vomiting and gastrointestinal distress including colic, gas and diarrhea. Occasionally asthma, allergic rhinitis and urticaria developed in the first few months. The rash which occurred in 85 of the 100 infants, subsequently proved to be allergic, was located on various parts of the body, more frequently on the face, buttocks and folds of the skin. It was often relieved by removal of feather pillows or an old mattress, wool, silk covering, toys and certain foods. Vomiting occurred in 24, usually associated with rash or colic. It was persistent and often projectile as in pylorospasm. Relief usually followed the elimination of orange juice, cod liver oil, milk or other common foods. Clein believes that it is possible to label 78 per cent of allergic children prior to age 4 months. As they grow older they develop perennial and seasonal hay fever, asthma, etc. The importance of early recognition is obvious, particularly with respect to the prevention, if possible, of later symptoms.

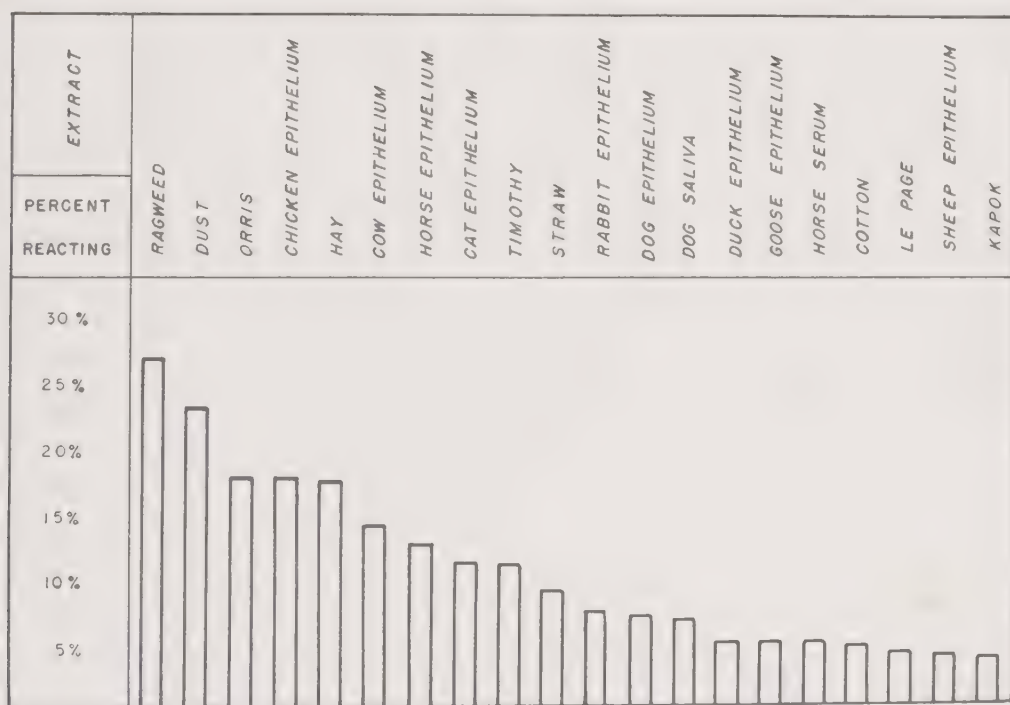


FIG. 10.—The importance of different inhalant allergens based upon percentage frequency of positive test reactions. Adapted from Cooke and Vander Veer. Pollens (ragweed and timothy) are easily the most frequent cause. The particular pollen responsible for symptoms varies, naturally, in different localities. Similar series by other investigators would show variations in the relative importance of others of the inhalants depending upon occupation, locality, exposure, etc., but the above series will be found fairly representative.

Inhalant and ingestant allergy. The statement has been made that young children are more likely to become allergic to foods; adults to inhalants—that around the period of adolescence a child loses his food allergy to become inhalant reactive. In my own experience this is not exactly the case. Young children are more often allergic to foods. Adults are allergic to inhalants in much higher percentage than are young children. But the adults do not lose their food sensitization to as great an extent as the above statement would lead one to infer.

In the adult with asthma or vasomotor rhinitis an inhalant allergen is usually found to be the primary etiologic agent. At the same time such a patient is usually found by test to be atopic to quite a variety of foods, and best therapeutic results follow the avoidance of not only the inhalant factors, but also the ingestants. When we are dealing with inhalant allergens in an adult, this may overshadow the food allergy, but the food sensitization may persist nonetheless.

Race Incidence

Available evidence would indicate that there is a distinct difference in racial predisposition to allergy. Here again we must realize that there are many factors besides race which determine whether persons in one or another geographic location will manifest symptoms. Furthermore, the accuracy of reports depends in a measure on the interest which the physicians of the locality take in the subject. Either John Bostock was wrong when, in 1819, he reported hay fever as a very infrequent disease, or else the condition is becoming rapidly much more common even in England. It seems probable that it was decidedly more common then than the literature would lead us to believe.

Scheppegrell concluded that hay fever is practically nonexistent in Mexico, populated chiefly with Indian and Spanish blood. However, when I investigated the situation in Mexico City I found that although hay fever is uncommon, due in great measure to the character of the vegetation, the diseases associated with food allergy were well recognized. The term allergy was not used locally because none of the physicians of the locality had had occasion to interest themselves in the subject. Scheppegrell concluded that there is no hay fever in Cuba. Durham's investigation explained this, since there is no ragweed, and practically all of the vegetation is cross-fertilized by insects. The same is undoubtedly true in great measure throughout the tropics.

Dr. Eugene Harvey of Bermuda has told me that on this island the only hay fever of importance is that due to cedar. He was under the impression that practically the only food allergy on the island was to sea foods. However, since becoming interested in the subject he has been surprised at the number of cases allergic to more usual foods. He has recognized a number of horse dander and house dust sensitizations. While he has made no survey he has concluded from his studies that allergy is not infrequent in Bermuda.

It becomes obvious that factors other than race may account for the infrequency (apparent or real) of allergy in any given group of people.

Thommen has studied the incidence of hay fever among the American Indians and appears to have shown quite conclusively that there is a racial variation. He interrogated persons directing the medical work on the Indian Reservations, finding that hay fever and asthma are rare in pure-blooded American Indians even though they are living in the same localities as whites who do suffer from these diseases, and are exposed to the same pollens.

He further states that although the native Javanese, Malays, and East Indians working on the rubber plantations in Sumatra, Dutch East Indies, and on the Malay Peninsula never have hay fever, Europeans and Americans who visit these territories do suffer when there. Natives in the hills of India rarely if ever suffer from hay fever, while Europeans and Americans do have the symptoms in that locality.

The Negro is subject to all of the allergic manifestations. No comprehensive survey has been made of this race, although the general impression has been that he is less allergic than the white race. Scheppegegrell found that hay fever is fairly prevalent in the Louisiana Negro, with at least one-third the incidence of that in the white race.

Derbes and Engelhardt (1943) surveyed the hospital population in Charity Hospital, New Orleans, for five years, and found the ratio of admissions of patients with bronchial asthma per one thousand admissions was in white males, 6.95; Negro males, 4.04; white females, 6.39; Negro females, 3.79.

The conclusion seems tenable, for the present at least, that although the apparent infrequency of allergy in races other than the white and even among the whites in various sections of the world is due in part to lack of "allergy consciousness" among local investigators, nevertheless the incidence among Caucasians appears to be actually higher than among other races.

CHAPTER X

CLIMATE, ENVIRONMENTAL FACTORS AND SOCIAL STATUS

Climate

Irrespective of environmental allergens and indeed long before allergy was recognized as a cause for hay fever or asthma, climatic factors were widely discussed. As early as 1698 Floyer expressed his opinion that changes in the weather, especially a falling barometric pressure, were likely to precipitate attacks of asthma. His experience was that moist air was injurious, dry air beneficial. That these nonallergenic factors are still worthy of consideration is shown by the investigations of Petersen (1934) who finds that deaths from asthma in Chicago occur more frequently during a *polar infall*, a change in cyclonic front in which there is a falling barometric pressure.

Barometric pressure.—The effect of barometric changes is seen in the experience of Rappaport, Nelson and Welker (1935) who reported that seven patients with pollen asthma in a pollen-free room experienced an "epidemic" of asthma on a day in which there were sudden weather changes but in which there was no increase in the exposure to pollen. On September 12, 1932, there was a sharp fall in barometric pressure followed by a rise and another fall, a sudden fall in temperature and a sharp rise in humidity. Heavy precipitation occurred late in the afternoon and again in the evening. That night all had severe asthma. Ten days later there was another rainfall but without great barometric change and with less pronounced change in humidity and temperature. On this second occasion none of the patients remaining in the pollen-free room experienced asthma.

Humidity, soil.—Salter (1860) concluded that low, damp areas with abundant vegetable life are unsuited for asthmatics. Van Leeuwen (1925) and Tiefensee stated that clay soil or soil containing large amounts of peat, a soil which is moist and does not allow the water to drain away readily, is likely to be bad for asthmatics. Asthmatics do better on sandy soil. In this case, probably humidity, and vegetable life play a part. Van Leeuwen found fungi the most important group of allergens in Holland. These are more likely to be abundant in such damp climates.

Too great humidity appears to be disadvantageous for asthmatics. Asthmatics are often worse in fogs. There are chronicles of three so-called epidemics of asthma occurring during an unusually heavy fog. It was said that persons who had never had asthma before experienced it at these times. The first occurred in Brittany in 1843, the second in London in 1880. The third is easily within our own memory since it received wide newspaper publicity at the time. It occurred in Belgium in 1932. It was said to have affected cattle also. I have a patient, living in New York City, who, in 1934, was at work in his office on the twentieth floor of an office building. In the midafternoon a heavy fog settled over New York. His lunch had been the same as usual, eaten at the same place, and there had been no change in his environment. With the settling of the fog, he rapidly developed very severe asthma which required repeated epinephrine injections for relief. Rowe has reported that patients suffering with asthma in San Francisco could go inland a few miles and promptly get relief. Black (1936) has called attention to the association of exacerbations of asthma with changes in the weather, and attempted to correlate weather conditions with

the blood density. He states that weather conditions influence the asthmatic person to such an extent that a food-sensitive person may continue to eat the offending food in the dry, hot weather of midsummer and suffer no ill-effects from it.

There are persons who cannot tolerate even a reasonably high humidity, one which would be normal for the average person. A woman in a Carolina cotton mill works in a large room in which the humidity is controlled mechanically and is registered graphically throughout each twenty-four-hour period. She conceived the idea that humidity might play a part in her asthma and discovered that as long as the humidity remained below 68 per cent she had no asthma. When she experienced asthma in the mill, she always found that the humidity had increased above 68 per cent. Sixty-eight was the critical point for her, determining the presence or absence of asthma, all other environmental factors remaining unchanged. On the other hand, Parlato has described five patients whose asthma was exaggerated in houses where the humidity was below normal. Thus, too little as well as too much may cause symptoms in different persons.

Altitude.—High altitude, especially on the European Continent, has long been vaunted as a cure for asthma. Van Leeuwen recommended an elevation of 4,500 feet or higher. He believed that the beneficial effects could not be attributed to escape from the allergens in one's home, situated at a lower altitude. One must be cautious in acceptance of this conclusion since as far as I can determine from the literature those who recommend high altitudes are practically without exception persons who live at low altitudes, practically at sea level. In Europe, outside of Switzerland and remote ranges such as the Pyrenees, there are few localities higher than 4,500 feet. As a consequence persons seeking altitude must change their allergenic environment very materially. One observation made by Bray, however, lends important corroboration to the conception of the beneficial effects of altitude. He states that members of the Royal Air Force who suffer from asthma gain relief from high altitudes. Contrary, we find that in the United States at altitudes of a mile or higher, hay fever and asthma do occur. Cunningham of Denver finds pollinosis a real problem. We are accustomed to think of Arizona as being an excellent climate for asthma and hay fever but in my experience benefit derived there is due either to a change in pollen exposures or to the dryness of the climate with its beneficial effect on sinus infection and bronchitis.

Whether or not high altitudes are beneficial in Europe because of change of environment or because of some factor intrinsic to the altitude, the fact remains that there appears to be quite general agreement in Europe that an altitude of over 4,500 feet is beneficial. A number of studies have been made to explain this. Explanations have included decreased exposure to dust, lowered moisture, and have even involved biochemical changes in the blood. Schneider (1921) found that the alkalinity of the blood was reduced at high altitudes. A relative alkalosis during allergic attacks has been described by some authors. The reduced blood alkalinity would, therefore, be beneficial. However, since the majority have failed to relieve allergic manifestations following the creation of definite acidosis, this must be accepted with decided reservations.

Burckhardt (1930) concluded that the only climatic factors which might play a part with persons already living in high altitudes were (1) sudden temperature changes and (2) increased humidity with fog, rain or snow.

Wind.—Humidity and barometric pressure changes are not the only climatic factors that may precipitate attacks, especially of respiratory allergy.

Van Helmont (1648) accused the east wind. Bray (1934) states that east winds in England are, in general, bad for asthmatics. I have two patients who, when living at Virginia Beach, directly on the Atlantic Ocean, experience vasomotor rhinitis or allergy when the wind is from the northeast. There is no land due northeast, although twenty to forty miles slightly east of north is the so-called "Eastern Shore" in which there is some marsh land. I have found from exposure of mold plates outside the windows that this northeast wind at Virginia Beach, during the time when these two patients were having symptoms, has a high mold content, although I have been unable to demonstrate sensitization to any of the molds that we have collected in this way. A child living in Wilmington, N. C., has symptoms when at the beach, and when the wind is from the east, with no land whatsoever to the east, and, surprisingly, is relieved when he goes inland about 10 miles. He is allergic to ragweed and has observed the above phenomena only during the ragweed season.

Prince (1935) found in Galveston that molds were of great importance in respiratory allergy in that locality and observed that when the wind is off shore, reaching the island from across marshes on the mainland, the mold content is high and the patient's symptoms are worse.

Wind alone may cause respiratory symptoms, but when the symptoms are attributed to wind from a given direction, one would do well to identify those substances for which the wind serves as vector.

Where a brisk wind alone is responsible for symptoms, this usually turns out to be an example of physical allergy, with sensitization to sudden changes of temperature such as that involved in the breathing of fresh cold air.

Temperature, actinic rays.—Heat, cold, sunlight, all may cause respiratory allergy and other manifestations, particularly urticaria, in a person who is not acclimatized to sudden changes. The person mildly sensitized to cold may have trouble only during the first cool days of the autumn. He may have no trouble during the colder days of midwinter, due to the fact that after a few cold exposures he has been able to adjust or acclimatize himself to the change. Another, mildly allergic, may have no trouble from the relatively slight changes of early fall but may get into difficulties in the more extreme cold of midwinter. Finally, one may be sensitized not so much to cold but to a change of temperature, a sudden change from warm to cold. This is the type of person who experiences symptoms during the summer when going into air-conditioned buildings, movies and the like. It becomes obvious, therefore, that a person allergic to cold may experience symptoms in the autumn, winter, spring, or summer. In midsummer he may get into difficulties when swimming in cool water. There is little doubt that many instances of sudden drowning of good swimmers are due to sensitization to cold. Horton, Brown and Roth have recently emphasized this point.

In the same way the person allergic to heat may have trouble only during the first warm days of spring, or when his tolerance is exceeded during the hottest days of summer, or even in midwinter when entering a heated building.

So-called sensitization to effort is probably sensitization to heat, manufactured within the body. Effort sensitized patients are usually also heat allergic. I have seen a woman who collapsed after swimming in a cold lake in the Maine woods. She avoids swimming for this reason. We did not find her sensitized to cold but did find her strongly sensitized to heat and effort. Her near-drowning was probably not due to cold sensitization but to the heat manufactured in the effort of swimming. She is also allergic to the actinic rays, an exposure of

two minutes under the quartz lamp at a distance of three feet resulting in generalized urticaria. Whenever she is at Atlantic City on the Boardwalk she has urticaria. This is, no doubt, due both to heat and the actinic rays. For years she has avoided exposing herself to the sun in a bathing suit.

Discussion.—Physical or climatic factors, wind, temperature, humidity, barometric pressure, all may cause allergic reactions in the predisposed. Temperature changes which inaugurate attacks in one person may relieve in another and vice versa. This is equally so with humidity. So far as I know, no conclusive studies have shown that a rising barometric pressure will cause symptoms in predisposed individuals, but by analogy, and because a falling pressure may do so, we must consider this as a probability. The North Carolina woman whose symptoms appear with rising humidity would do poorly at Mont Dore, that famous French spa where asthmatics remain in rooms filled with vapors from the steaming hot springs. Since there must be others who are allergic to increased humidity, it seems probable that a proportion of those who attempt a cure at Mont Dore find their symptoms made worse rather than better.

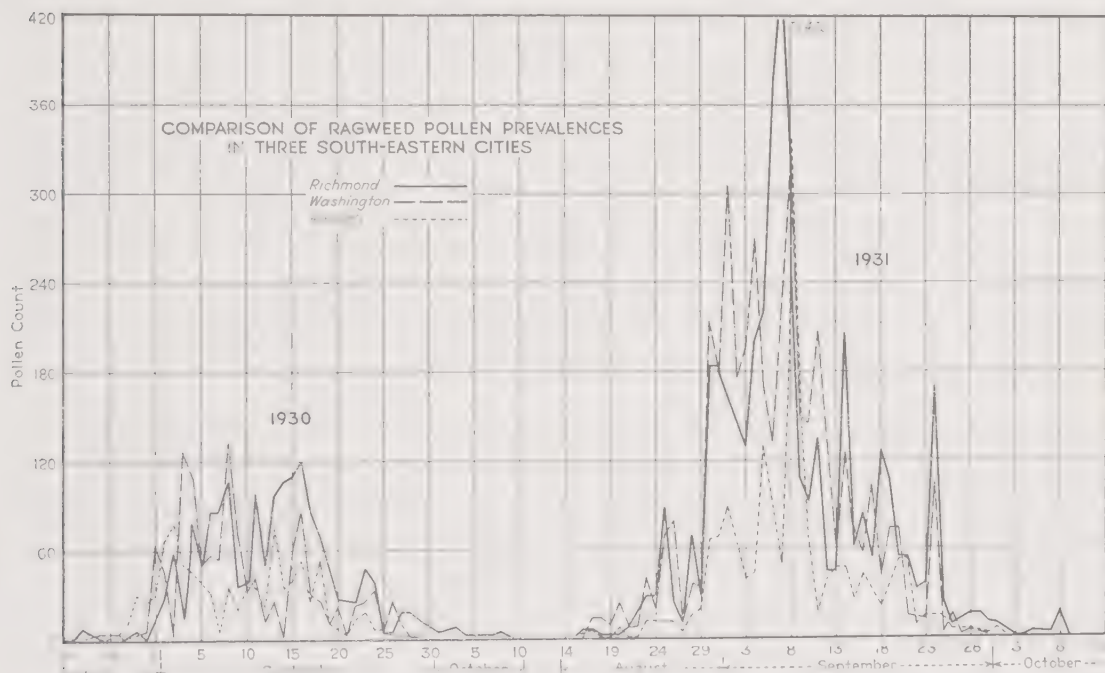


Fig. 11. Pollen counts on two successive years in three cities, situated approximately equally distant on a roughly straight line extending 250 miles north and south. The curves show some variation from day to day, due principally to local weather conditions. At the same time the general character of the curve for the two years shows great similarity between the cities, 1930 being a year of low prevalence, 1931, one of high prevalence. More general climatic factors such as conditions during the growing season determine the total pollen yield for the season and may be reflected similarly in localities hundreds of miles apart.

It was a wise precept formulated by Hyde Salter, sixty-five years ago, that asthmatics do best in climatic surroundings which are the reverse of those to which they are accustomed. The asthmatic in Arizona might find relief in southern Florida, while the asthmatic from Miami is being relieved in Tucson. Fortunately, today, we can control the climate at home, to a degree, provided we have determined the conditions best suited to the individual.

Environment

Botanic flora. In the majority of allergic patients, factors usually considered as climatic are actually dependent upon specific environmental allergens.

which in their turn may depend upon the climate. A hay fever sufferer living on the Eastern Seaboard or in the Mississippi Basin may find the climate of California ideal for his malady. However, it is not the climate alone but the fact that ragweed to which he is sensitized grows abundantly in the East, not at all on the West Coast. There are many places where the ragweed sufferer may find relief: in the woods of Canada or northern Michigan, on the Pacific Coast, in Cuba, Bermuda or on an ocean voyage. The "climate" is salubrious but only to the extent that it is insalubrious for the development of certain flora.

Hay fever resorts. Nor is the climate alone responsible for the flora. The hand of man plays its part. Most of the hay fever resorts of preceding generations have lost their ability to relieve. Situated as they were, well away from civilization, in the heart of large timbered areas, where the only pollens of consequence were those from trees, where weeds and grasses had no opportunity to grow, they provided ideal havens for the victim of sensitization to the pollens of weeds and grasses. Of course, the tree pollens were there but the trees pollinate early, before the grass and weed sufferers arrive. Therefore, even if the latter were allergic to certain of the tree pollens they would have no trouble while there.

Unfortunately the popularity of these resorts was their undoing. The hay fever sufferer longed for greater ease and comfort than could be obtained in a tent alongside a woodland stream or on the shore of a lake. Resorts sprang up, with their fine hotels. In order that sustenance might be provided, trees were felled and acres tilled. Whereupon weeds and grasses commenced to grow. The hand of man had played a part.

The hand of man has played some part in determining the absence of ragweed hay fever in Europe. Because of the intensive cultivation of the soil, weeds are less abundant. Pollinosis in Europe is due to sensitization to the trees and grasses.

Geography and flora. One might well wonder why, with all of our trans-continental traffic, ragweed has not thrived in California. Here, however, it is the climate that prevents. Ragweed has actually been imported into southern California and is being grown on a small tract of land for the purpose of collecting pollen. Although several years have elapsed since this was done, ragweed has not run wild. The weed grows late in the season, blooming after midsummer. In the East the growth-promoting rainy season is much later than in California. West Coast rainfall occurs in November, December and January, long before it is of any use to ragweed. This plant must have an abundance of water at the proper time for it to flourish. Even in the pollen gardens where it has been planted in southern California, diligent artificial irrigation is employed to save it from perishing.

Among our routine pollen tests I have for years included the pollen of sugar beet. We find a large number of persons allergic to this but have never traced a case to sugar beet pollen as the etiologic agent in Virginia. However, Dutton tells me that in El Paso, sugar beet pollinosis is a very troublesome factor among those who cultivate the plant. This would be the case elsewhere where beets are raised in large quantities.

I have said that cedar is the chief pollen factor in Bermuda. While in the eastern portion of the United States we do find persons sensitized to cedar or juniper it is not an important factor. But as we go west we find it a factor of decided importance in Texas, due to the prevalence of the mountain cedar and in the region of Santa Fe where the closely related juniper thrives.

Fungi.—These examples are sufficient to demonstrate the environmental importance of the pollen in the air, both in its qualitative and quantitative aspects. The same is true although to a lesser degree with fungi. Balyeat has shown that in late summer the concentration of mold spores in the air far exceeds that of pollens. Since fungus sensitization is not as common, it is only in those areas where concentration is unusually heavy that we find mold allergy a major problem.

Storm Van Leeuwen (1927) first emphasized the importance of fungi. Holland is a low, damp country and he found fungus allergy the most outstanding single etiologic agent in the respiratory cases. Fifty per cent of asthmatics in that country give positive skin reactions to the air-borne fungi. Jimenez Diaz (1932) states that fungus allergy is important in the coastal region of Spain. Prince, in the Texas coastal region, Feinberg, about Lake Michigan, and Wittich, in the grain country in and about Minnesota, have found this true, as has Metzger on the west coast of Florida. In Virginia we find mold sensitization a factor of importance especially in the old colonial homes with damp cellars situated along the river banks of the tidewater section.

House dust.—House dust is an environmental factor of extreme importance. House dust differs quite essentially from road dust. Much of its allergenic constituents are derived from the disintegration of material from animal and vegetable sources, the silk, wool hairs, cotton and linen fibers of draperies, upholstery, rugs, clothing, and from feathers, horse hair, rabbit hair and the like, constituents of pillows, kapok, upholstery, felt, etc. Pollen, fungi, bacteria and many other things combine to form the constituents of house dust. Nevertheless, irrespective of the individual constituents of house dust, sensitization appears to be a very specific and very common malady. What it is in house dust which acts as the antigen is still not known. It seems to be the same in all parts of the country, so that dust collected in one locality may be used as antigen in another. There is no way completely to avoid it, even with the most scrupulous cleanliness.

Environmental factors and foods.—Household pets and barnyard stock often constitute most important items in the environment. Cosmetics, insecticides and tobacco are other outstanding examples. Foods may well be considered also as environmental factors since they are substances with which the individual comes in contact from the outside. Not long ago, texts listed those foods to which persons had been found sensitized. Today it would be much shorter to list those foods to which man has not been found allergic. Indeed, it would appear that under appropriate circumstances man may become allergic to any known article of nourishment.

Occupation.—Occupational allergens are most numerous and are continually being added to, chiefly in the form of new chemical compounds. Although the dermatoses possibly constitute the largest proportion of manifestations of occupational allergy, inhalant allergy comes in for its full share. This phase of the subject will be discussed elsewhere, but it is obvious that here also we are dealing with environmental factors.

Social Status and Intellect

One often sees the statement that allergy is a disease of "the better classes," the well-to-do and the higher strata of society. This conception is far from new. Thommen has collected the old literature on the subject. He tells us that Bostock could not find "a single unequivocal case among the poor." Phoebus

(1862) found much more hay fever proportionately in the noble born than in the general citizenry. One hundred and forty-six of his hay fever patients were educated, 8 uneducated. Beard (1876) found Fifth Avenue quite familiar with hay fever but not a case in the slums. Yonge as recently as 1910 stated "the malady is practically confined to the educated classes."

Today we find allergy in all of its manifestations, in all social groups, and apparently with very little variation among the groups. My own survey of a community of 508 persons in which I found 10 per cent suffering from major allergy, which was the highest percentage reported up to that time, dealt with a small farming community with a few gas stations and general stores and no one of even average wealth, as compared with the usual urban populations.

Balyeat (1928) has suggested that allergic children are above the average mentally and are freer from diseases other than allergy. His criteria for freedom from other disease might be subject to criticism. A physical examination and laboratory studies were made, but the outstanding criterion was the history of past infectious diseases of childhood. With regard to these much depends upon the opportunity for exposure.

However, with these criteria Balyeat concluded from a study of 323 children that 78.35 per cent were above normal in general health, 16.7 per cent normal and 4.95 per cent subnormal. The above-normal cases had had practically no diseases of childhood; the average normal had had what the author considered the average number of diseases of childhood, of moderate severity; while the subnormal group included those who had had a larger number of contagious and infectious diseases than usual "and who seemed somewhat delicate in general."

Mental ability.—Balyeat also studied the mental activity of 80 nonallergies. Among the allergies 68.75 per cent were mentally superior, contrasted with 25 per cent among nonallergies.

This is to be contrasted with the indirect evidence supplied by Shannon who found that allergic children exposed to their specific allergens did poorly in school. Following relief by avoidance their work improved greatly. There was no comparative study of intelligence quotients.

In a more recent study of 145 allergic children and 145 nonallergic controls whose intelligence rating was determined by four different psychologic methods, Piness, Miller and Sullivan found that:

1. Children with asthma are very similar in intellectual level to a normal group with the variations of a normal group. They include children of superior, average, normal, and inferior intelligence.

2. There might be some indication that the incidence of allergy is less in the feeble-minded group, but the data available are very general and not statistically reliable.

3. As far as school success is concerned, the allergy group is similar in grade placement to the normal group.

4. There is evidence in the allergic group of slightly more school retardation than should be expected if their illness had not handicapped them.

CHAPTER XI

HEREDITY

It is now quite generally agreed that there is an hereditary factor in allergy, the allergic tendency being at least in part inherited. The children of allergic parents are more liable to develop the malady, and at an earlier age, than the children of parents who appear to be nonallergic.

The first serious modern study of the heredity of asthma and hay fever was undertaken by Cooke and Vander Veer (1916). There followed the work of Adkinson (1920), of Spain and Cooke (1924), of Bray (1930) and of Richards and Balyeat (1933).

Early observations.—While these and the more recent work of Wiener, Zieve and Fries which we shall discuss in greater detail, comprise the most comprehensive efforts to determine the method of inheritance, the conception of an hereditary factor is by no means new. As early as 1650 a family incidence of asthma was discussed. Similar suggestions were made concerning hay fever twelve years after its first description by Bostock. The family incidence of angioneurotic edema was discussed in the same year in which Quinke described the disease.

The term migraine first appeared in English medical literature in 1777. Modern recognition of the disease as an independent symptom complex dates from 1784 when Tissot described the condition in his *Dictionary of Medicine*. It was not until fifty years later that he discussed the occurrence of the disease in successive generations, but I suspect that he and probably others had this in mind long before the appearance of his later article.

TABLE III. ALLERGY AS AN HEREDITARY DIATHESIS. SHOWING AUTHORS AND DATES ON WHICH THEY PRESENTED EVIDENCE OF AN HEREDITARY FACTOR IN SEVERAL ALLERGIC DISEASES

ASTHMA		HAY FEVER		MIGRAINE		ANGIONEUROTIC EDEMA	
Sennertus	1650			First classified as an independent disease by Tissot 1784			
Floyer	1698						
Cullen	1784						
Ryan	1793						
Davidson	1795						
		Disease first described by Bostock 1819					
Eberle	1831	Elliotson	1831	Tissot 1834			
Ramadge	1835			Symonds 1858			
Andral	1839						
Salter	1860	Wyman	1872	Liveing 1873			
		Beard	1876			Disease first described by Quinke 1882	
Stevenson	1879			Heuchen	1881		
Geddings	1883	Mackenzie	1884				
				Moebius	1894		
Drinkwater	1909						
				Auerbach	1913	Strubing	1885
Cooke & Vander Veer	1916	Cooke & Vander Veer	1916			Osler	1888
Adkinson	1920						
Spain & Cooke	1924	Spain & Cooke	1924	Smith	1922		
Richards & Balyeat	1933	Richards & Balyeat	1933				
Bray	1934						

TABLE IV. FAMILIAL INCIDENCE OF ALLERGY

ASTHMATIC CHILDREN WITH POSITIVE FAMILY HISTORY	
Rowe	70.9%
Bray	68.5%
Comby	58.0%
Bullen	50.7%
Schloss	47.0%
Peshkin	42.5%
40-70 per cent of asthmatic children present a family history of allergy	
ASTHMATIC ADULTS WITH POSITIVE FAMILY HISTORY	
Van Leeuwen	63.6%
Rackemann	
Extrinsic	58.7%-47%
Intrinsic	10.7%-37%
Two surveys, 1920 and 1927	
Rowe	58.4%
Adkinson	48.0%
Coke	46.0%
Menagh	40.0%
Bullen	39.4%
Salter	39.0%
40-60 per cent of asthmatic adults give a family history of allergy	
HAY FEVER PATIENTS WITH RESPIRATORY ALLERGY IN FAMILY	
Sajous	37.0% of relatives have hay fever
Sajous	18.0% of relatives have asthma
Scheppegregell	35.8% of relatives have hay fever
Kahn	80.0% of relatives have hay fever
Spain & Cooke	58.4%
Cooke & Vander Veer	48.4%
35-80 per cent of hay fever patients give family history of inhalant allergy	
Total 55%	
MIGRAINE PATIENTS WITH ALLERGIC FAMILY HISTORY	
Rowe	74.0%
Bray	82.0%
Balyeat	85.4%
Vaughan	85.0%
75-85% of migraine cases have allergy in the family	
FAMILY ALLERGY INCIDENCE IN OTHER DISEASES	
FOOD ALLERGY	Rowe 68%
ECZEMA	Piness & Miller 41%
	O'Keefe (children) 28%—(adults) 37%
	Rackemann (children) 36%—(adults) 50%
	Rowe 69.0%
	Balyeat 76.6%
URTICARIA	Menagh 32.6%
	Rowe 55.0%
	Rackemann & Colmes 25%

Osler as early as 1888 described 22 cases of angioneurotic edema in five generations of a family. Similar descriptions have appeared since that time. Bray remarks that ichthyosis occurs in about 5 per cent of asthmatic children and that other members of the family are frequently affected. Spangler has reported a high incidence of allergy in the families of epileptics.

Stiles and Johnston (1946) studied five generations of a family containing 232 persons. Respiratory allergies were found in 22.4 per cent of these, as compared with 7 per cent in the normal population. They believe that respiratory allergy may be an irregular dominant characteristic. Tables III and IV show that overwhelming evidence points to allergy as a familial disease.

Objections. Although it is quite generally agreed that inheritance plays a part in the development of the allergic predisposition, this conclusion is not universal. Ratner in particular has questioned the conclusion. He found in a study of 250 allergic children and 315 normals that the family incidence was approximately the same in both, and that about 50 per cent of families in both groups showed no allergy.

Difficulties.—The fact that in from 40 to 50 per cent of cases a definite inheritance cannot be demonstrated has been used as an argument against the hereditary theory. However, as Walzer, Coca and others have pointed out, negative evidence, particularly in this regard, is not as convincing as positive evidence. Relatives who should present a history of allergy may be potentially allergic, and manifest the disease at some period later than that of the questioning. In this way children often manifest their allergy before one or both parents do so. As Walzer points out, ignorant parents may deny having the disease although they actually have it, due to the feeling that the admission is tantamount to an acknowledgment of responsibility for the disease in the child. Sometimes parents have mild allergic symptoms which they do not recognize as allergic. In this case the denial is honest but incorrect. This would apply for example to the parent of an asthmatic child who fails to recall that he himself developed diarrhea following the eating of walnuts.

General conclusions concerning inheritance. I shall make no attempt to record here the exact figures reported on the family incidence of allergic diseases. All are different and many are not directly comparable because of differences in the methods employed in statistical classification. Only the general conclusions agreed on by the majority of investigators are presented.

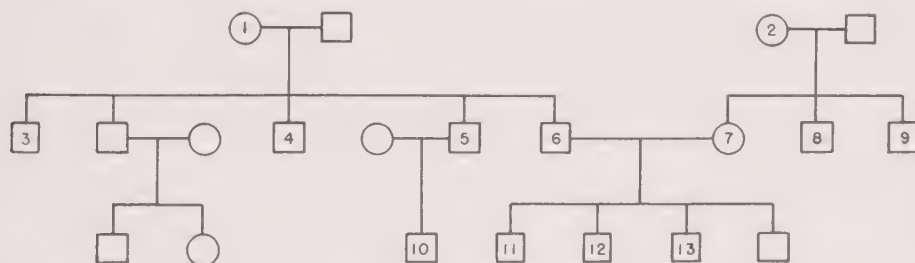


Fig. 12.—An allergic family tree. The union of two allergic families produces allergic offspring. There is no evidence in this tree of the inheritance of a tendency to involve specific shock tissues. All of the common allergic symptoms appear. The inherited trait appears to be "a tendency to become sensitized." The shock tissue which will become involved cannot be predicted from the inheritance. In the same way there is no obvious inheritance of sensitization to any given allergen, a large miscellaneous list appearing in the three generations.

1. Hay fever due to daisy and goldenrod. Abdominal allergy from clams and chocolate. 2. Migraine, cause undetermined. 3. Urticaria from quinine. Death from drowning (physical allergy?). 4. Colitis and diarrhea due to milk. 5. Nasal allergy from house dust. Trichophytid. 6. Abdominal allergy from mushroom, peach, and almond. Urticaria from wool and strawberry. Headache from shrimp. 7. Spastic colitis, urticaria, and eczema from wheat and cantaloupe. 8. Gastrointestinal allergy from walnut. 9. Hay fever due to ragweed. 10. Horse asthma, ivy sensitization, gastrointestinal symptoms from milk. 11. Canker sores from chocolate. Asthma due to ragweed. 12. Asthma due to feathers, dust, and ragweed. Eczema and asthma due to wheat, chocolate, and strawberry. 13. Nasal allergy from pyrethrum. Serum sickness due to scarlet fever antitoxin.

Antecedent family history of allergy is positive in from 50 to 75 per cent of allergies. This is especially true with adults where the relatives have lived long enough to develop symptoms even at relatively advanced ages (Cooke and Vander Veer, Rackemann, Rowe, Peshkin, Bray, Comby, Bullen, Schloss, Balyeat, Smith, Allen, Hansel). This high incidence of family allergic history in allergies is to be contrasted with the low antecedent family history found in normal non-allergic persons (7 per cent).

Not only does an allergic heredity predispose to the disease but in some measure it predetermines the age at which the individual will manifest symptoms. Nearly all allergies with bilateral inheritance, through both mother and father, will manifest the disease before age ten. Only about one-third of those with unilateral inheritance and one-fifth of those with no recognized inheritance develop their first allergic symptoms prior to age ten.

The heavier the allergic inheritance, the greater is the number of offspring who will develop allergy. The heavier the inheritance, the earlier will be the ages at which the symptoms appear. It has been estimated that nearly three-fourths of all children with bilateral allergic inheritance will eventually develop the disease. About one-half of those with unilateral inheritance do likewise. The heavier the inheritance, the greater will be the number of different allergic manifestations in each of the offspring.

There appear to be two modes, statistically speaking, for the age of first development of allergy. These are divided by puberty. The largest number develop symptoms during the first decade, which represents the first mode. In the third decade there is also a decided increase in the incidence of the first attack although, of course, first attacks are recorded for all ages. However, there appear to be two chief times for onset, prior to puberty and in the first decade or two thereafter.

Some authors (Bray, Rowe, Hansel) conclude that inheritance is greater through the mother than through the father. On statistical grounds I feel that this conclusion should be studied further before receiving entire acceptance. So many factors play a part in predetermining the type of material available for statistical study. A child is usually brought to the clinic by the mother rather than by the father and the mother would be more conscious of her own symptoms, especially minor or evanescent symptoms, than of those of her husband.

What we inherit.—It is generally agreed that it is not the allergic manifestation of the moment which is inherited but rather the *tendency to become allergic*. The parent may have asthma while the offspring may have hay fever, urticaria, migraine, or others of the clinical allergies. It should be noted, however, that Coca and Clarke, Donnelly, and Coca, have stated that the allergic children of asthmatics express their allergy more often in the form of asthma than in other possible modes. This has also been mentioned in the literature as frequently being a characteristic of hay fever, migraine, angioneurotic edema and eczema. They therefore suggest that the inheritance may include the predisposition to react on the part of one or another of the shock tissues. Coca suggests that there may even be some hereditary factor that determines to a degree at least the substance to which one will become allergic.

Here again statistical studies have not been sufficiently comprehensive to be conclusive and for the present it is safer to say that the predisposition to become allergic is inherited but that the substance or substances to which one becomes sensitized and the manner of the allergic expression are determined, after birth, by a variety of factors such as constitutional makeup, local irritation, and the nature and prevalence of allergens in the immediate environment. The inheritance of sensitization to ragweed would be a logical concept as long as one held to the theory that experimental anaphylaxis and clinical allergy are two entirely different phenomena, the second being primarily hereditary. But to those who accept a common basis for both, the inheritance of sensitization to ragweed does not fit into the picture nearly as well as an inheritance of a predisposition to become allergic to some substance to which one is exposed during gestation or after birth. Clinical evidence indicates that the substance to which one becomes sensitized depends in great measure upon the opportunity for exposure and the length or intensity of the exposure.

Theories of the Mechanism of Inheritance

Cooke and Vander Veer, Spain and Cooke, and Bucher and Keeler have favored the idea that allergy is inherited as a simple Mendelian dominant.

Adkinson concluded that allergy was a recessive characteristic. Richards and Balyeat expressed their opinion that it is inherited as a partial dominant.

Bucher and Keeler have reported an allergic study of five generations in a single family, representing 454 individuals of whom 236 were males and 218 females. Of the total number, 102 manifested allergy. From their study they conclude that this particular family transmitted allergy as a simple dominant unit-character affecting in equal numbers both males and females. There was about a 12.5 per cent deficiency in the allergic classes, due to normal overlaps. The commonest allergic manifestations were asthma (49 per cent of the allergic individuals) and hives or eczema (42.1 per cent). Seventeen and six-tenths per cent of the allergic members of the family exhibited multiple manifestations of allergy.

Wiener, Zieve and Fries have presented what appears to me the most logical explanation of the allergic inheritance.

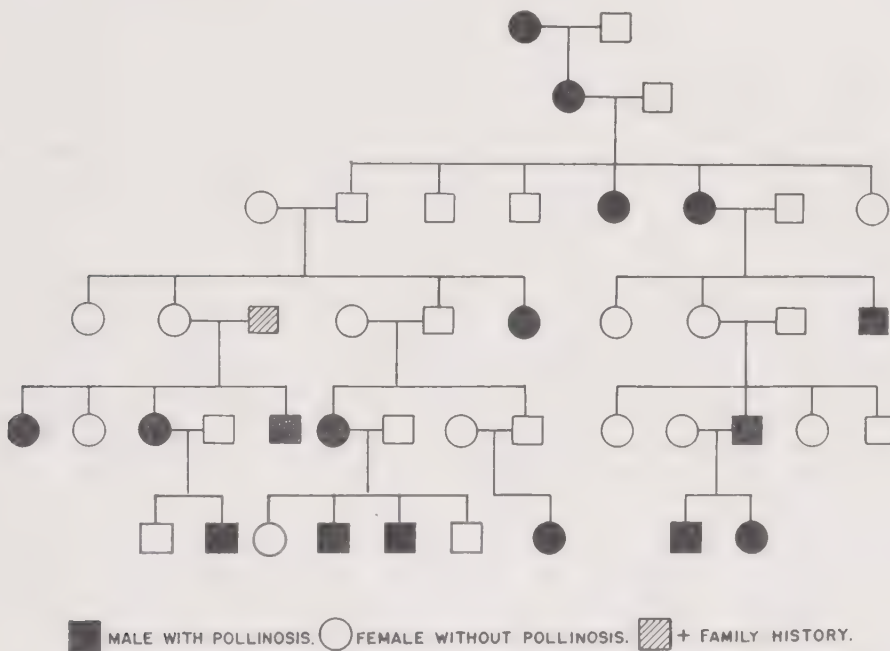


Fig. 13.—Record of the inheritance of pollinosis in six generations. This would at first suggest the inheritance of a predisposition to involvement of certain shock tissues (respiratory tract). However, the family records are limited to hay fever and asthma and do not specify presence or absence or other allergic symptoms. The two members of this family group, studied by the writer, did have other allergic symptoms.

Recessive genes.—They discard the dominant theory since this fails to explain why, in more than half of the pedigrees, both parents are normal. They reject the recessive theory since there are pedigrees in which both parents are affected and some of the children are normal. Their theory inclines more to the recessive theory of Adkinson but explains why two allergic parents may have apparently normal children.

There are two modes of allergic symptoms, before and after puberty. Cooke and Vander Veer, also Spain and Cooke have shown that when both parents are affected, the children manifest the disease at an early age, usually before puberty. Where one is affected the children usually develop symptoms later. Where neither parent manifests allergy, symptoms appear still later. Wiener and his collaborators classify allergies into two categories, those who develop

first symptoms before puberty, and those who do so later. Those before puberty have bilateral inheritance. Those after puberty have either unilateral or no obvious inheritance.

According to them, the heredity of allergy depends upon a single pair of allelomorphic genes; N—the normal or nonallergic gene which tends to be dominant; and A—the allergic gene tending to be recessive. Genes are inherited, half from the mother and half from the father. Since each possesses two genes and since each offspring possesses two genes, the extra two obviously

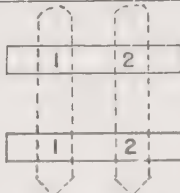
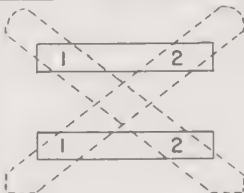
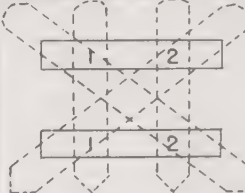
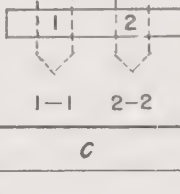
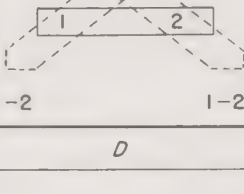
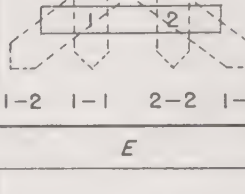
	<i>A</i>	<i>B</i>	<i>A - B</i>
PARENT I			
PARENT II			
CHILDREN	1-1 2-2	1-2 1-2	1-2 1-1 2-2 1-2
	<i>C</i>	<i>D</i>	<i>E</i>
PARENT I	N — N	N — N	N — A
PARENT II	N — N	N — A	N — A
CHILDREN	NN NN NN NN	NN NN NA NA	NA NN AA NA
	100% N	50% N 50% NA	25% N 50% NA 25% A
	<i>F</i>	<i>G</i>	<i>H</i>
PARENT I	N — N	A — A	A — A
PARENT II	A — A	N — A	A — A
CHILDREN	NA NA NA NA	NA NA AA AA	AA AA AA AA
	100% NA	50% NA 50% A	100% A

Fig. 14.—Possible mechanism of the inheritance of the allergic predisposition. Inheritance is accomplished by the union of one gene from one parent with a similar gene from the other parent.

Parent I (Block A) has a single pair of allelomorphic genes, 1 and 2. Parent II has a similar pair. Union is accomplished by the combination of one of the two genes from parent I with one of the two genes from parent II. The two remaining genes are discarded. Block A and Block B show the possible combinations, which are summarized in Block A-B. No other combinations are possible. Applying this in allergy, gene A determines the allergic constitution; gene N is the contrasting normal gene.

If there are no allergic genes (Block C) there will be no transmission of allergy. If all genes are allergic (Block H), all offspring will be allergic. AA may be considered as representing those who are highly allergic, major allergies, or allergies developing symptoms before puberty. NA may be considered the minor allergic, mildly allergic, those who develop symptoms after puberty, or those who never develop symptoms but are potentially allergic and pass on the inheritance to their offspring.

Many interpretations of the chart are possible. Thus in Block E we may be dealing with two persons who have never had clinical evidence of allergy, or one mildly allergic and one clinically nonallergic, or with two mild allergies. The offspring of all three of these combinations will have the same distribution of allergy.

Approaching the analysis from another angle, let us take four different unions of one who is clinically nonallergic, with an allergic. Will the offspring from these four different unions all show the same distribution of allergy? Since they may represent Blocks D, E, F, and G it is possible that none of the four unions will manifest the same distribution in the offspring. The same applies to the union of two who have never shown clinical evidence of allergy. This does not necessarily fall in Block C, since D or E might equally well be represented by persons who have never been obviously allergic. Finally, union of two allergies does not necessarily imply Block H but may be represented by Blocks E and G.

are discarded. In Fig. 14 *a* and *b* are shown the four possible ways in which genes may be combined in the offspring. Parent 1 has a normal gene which we may for the purposes of the present discussion call dominant, and a recessive allergic gene. The same is true of parent 2. With four matings the four possible results will be one child with two normal genes, one with two allergic genes and two with a combination similar to that of the parents themselves.

According to the hypothesis a person with two allergic genes will develop symptoms prior to puberty. A person with two normal genes will never develop allergy. The person with mixed genes is a potential allergic and either will develop symptoms after puberty or will go through life without symptoms, but still transmitting this gene to the next offspring.

Possible combinations.—The remaining figures show the various possible combinations. The directions of the arrow indicate the directions of possible crossing as brought out in *a* and *b*. Figure *c* shows that two normal mates with no allergic genes can have only normal children. In figure *d* one normal is mated with one potential allergic. The result will be two normals and two potential allergies who may or may not have yet developed symptoms. In the four possible offspring are one nonallergic, one allergic prior to puberty and two potentials. In figure *f*, the mating of a normal with a frank allergic, all of the four offspring will be potential allergies. Figure *g* shows that one frank allergic mating with one potential allergic will result in two potential allergies and two frank allergies. Finally, two frank allergies, mating, figure *h*, will produce children all of whom develop allergic symptoms prior to adolescence. These are all of the possible combinations.

In discussing the possibilities of mating one should bear in mind that an N-A parent may be normal or may become allergic, especially after puberty. Bearing this in mind there are several possible results of mating.

1. **Both parents normal.**—This is represented by figures *c*, *d*, and *e*. Twenty-five per cent of the offspring in *e* will be frankly allergic. Fifty per cent of those in *d* and *e* are potentially allergic and may manifest symptoms in later life. Of 12 matings (*c*, *d*, *e*) one will be allergic before adolescence, four, or one-third, are potentially so after puberty, and seven inherit no allergy.

2. **One parent allergic, the other normal.**—This is represented by figures *d*, *e*, *f*, and *g*, assuming that the second parent, in figure *e*, who is potentially allergic, has manifested symptoms. In *d*, as we have seen, 50 per cent of the offspring will be potentially allergic; 100 per cent will be so in *f*; 50 per cent in *g*; while an additional 50 per cent in *g* will be frankly allergic. In figure *e* we find that 25 per cent are frankly allergic, 50 per cent potentially so.

3. **Both parents allergic.**—This is represented by figures *e*, *g*, and *h*.

Calculated predictions. On the basis of the theory it is possible to predict what proportion of children from any mating will develop allergy and whether the symptoms will appear before or after puberty. The authors compute that from one-fifth to one-sixth of the potential allergies (N-A genotype) will develop allergic symptoms. The remaining 80 to 85 per cent go through life without allergy but do transmit the gene to their offspring. Whether or not their offspring will manifest allergy will depend upon the gene of the mate.

The authors reach their conclusion that between one-fifth and one-sixth of the N-A population will eventually develop allergy by a mathematical calculation based upon the statement of Cooke and Spain that 7 per cent of the general population develops allergy. One third of allergic cases begin with symptoms before puberty. Therefore, the frequency of genotype A-A is one third of 7 per cent or 2.3 per cent. They calculate from this that the frequency of geno

A is 15 per cent. Consequently the frequency of gene N in the general population is 85 per cent. Using these figures in a complicated mathematical formula they calculate that 18 per cent of heterozygous individuals, individuals carrying dissimilar genes, N-A, will develop allergic symptoms. The remainder, 82 per cent, will not. Of the apparently normal population (N-N plus asymptomatic N-A), 22 per cent are carriers of the abnormal gene A and are, therefore, potentially allergic.

Since the rationale of these calculations is rather involved, I quote this portion of the article by Wiener et al. verbatim, for those readers who wish to follow each step of the analysis. It should be noted that for simplification I have used the letter N to indicate the normal gene, A the allergic gene. In the original article however, the normal gene was indicated by H, the abnormal or allergic by h. Therefore, in the following, HHH indicates normal, hh allergic, and Hh potentially allergic, mixed or heterozygous.

“Frequencies of the various possible genotypes and phenotypes.—According to Spain and Cooke the incidence of allergic disease in the general population is approximately 7 per cent. Since one-third of the cases of allergy have their age of onset before 10 years the frequency of genotype hh can be assumed as 2½ per cent.

“If we let x equal the frequency of gene h in the general population, then assuming panmixia

$$x^2 = 0.0233,$$
$$x = 0.152 \text{ or about } 15 \text{ per cent}$$

“Hence, the frequency of gene h in the general population is 15 per cent, and of gene H, 85 per cent. Of course, the relative frequencies of the two genes is not the same in every country and race, since the incidence of asthma varies in different parts of the world just like the incidence of other hereditary characters, e.g. blood groups, eye color, etc.

“From the frequencies of the genes H and h it is possible to recalculate the frequencies of the various genotypes and phenotypes as follows:”

GENOTYPE	FREQUENCY	PHENOTYPE	FREQUENCY
hh	$x^2 = 2.33\%$	Allergic before puberty	2.33
Hh	$2x(1 - x) = 25.5\%$	Allergic after puberty	4.67
			} 7%
HH	$(1 - x)^2 = 72.25\%$	Apparently normal	20.83
		Pure normal	72.25
			} 93%

“It is clear, therefore, that on the average only $\frac{4.67}{25.5}$ or 18 per cent (that is, between one-fifth and one-sixth) of the heterozygous individuals develop allergic symptoms. However, this percentage is not a fixed one but will vary from one family to another, depending upon environmental conditions. Of the apparently normal population, $\frac{20.83}{20.83 + 72.23}$ or 22 per cent, that is, more than one-fifth, are carriers of the abnormal gene h and are, therefore, potentially allergic individuals.

“It is now possible to calculate the frequency of a positive antecedent history among the apparently nonallergic individuals in the general population. From Table II 85.49 per cent of pure normal individuals, 53.59 per cent of individuals of genotype Hh have a negative family history. Among the normal population, about 22 per cent belong to genotype Hh, and 78 per cent to genotype HH. Hence, the chance of a negative history among apparently normal individuals is $(0.22)(0.5359) + (0.78)(0.8549) = 0.7847$, or approximately 78.5 per cent. Therefore, it is to be expected that as many as 21.5 per cent of apparently non-allergic individuals would give a positive antecedent history, either direct or collateral.”

Discussion.—The accuracy of these figures depends upon the accuracy of the conclusion reached by Spain and Cooke, that “the incidence of allergic disease in the general population is approximately 7 per cent.” If this figure is too small, conclusions concerning the frequency of the genotype must be revised accordingly. There is one obvious fallacy in accepting this figure since

Spain and Cooke's conclusions were based primarily upon a study of the family incidence of hay fever and asthma, not of allergy in general. Wiener and his collaborators apply this, as quoted above, to allergic disease in general.

We have found that 10 per cent of a selected population are frankly allergic, and that an additional 50 per cent suffer from evanescent or minor allergy. Among the major allergies I do not distinguish between those who had first symptoms before puberty and those after puberty. Sixty per cent is a much higher figure than would be considered possible from the table by Wiener et al. reproduced above. According to the table the largest possible number of allergic persons in a community would be 27.83 per cent (the first three figures of the second *Frequency* column), and even this figure would not be reached unless every person with an allergic gene showed symptoms.

Other possibilities.—If, instead of accepting the figures of Spain and Cooke, of 7 per cent incidence for hay fever and asthma, we accept those of the writer of 10 per cent incidence for major or frank allergy, we find from the following table that 34.17 per cent of the population carries the allergic gene. This recalculation assumes that the statement is correct that one-third of allergies have onset before age ten. This assumption again is based chiefly on studies of respiratory allergy, and I believe that the percentage should be very materially increased for allergy in general, although I have no statistics and know of no other statistics that would decide this question.

GENOTYPE	FREQUENCY	PHENOTYPE	FREQUENCY
AA	$x^2 = 3.33\%$	Allergic before puberty	3.33
NA	$2x(1-x) = 29.83\%$	Allergic after puberty	5.66
		Apparently normal	24.17
NN	$(1-x)^2 = 65.83\%$	Pure normal	65.83
			10% } 90% }

The logic of the inheritance of allergy as developed by Wiener and his collaborators appears to be sound and, in a very rough way, consistent with the available statistical surveys. All surveys have been made on selected groups and the total number in each survey is never large enough for final statistical conclusions. The surveys may be looked upon as representing trends, but none of them can be considered as having been large enough to eliminate the factor of variables.

A major premise of Wiener's hypothesis is that A-A genotypes develop symptoms prior to adolescence while mixed types do so later, if at all. This is an arbitrary conception. Another, equally arbitrary and equally logical, would be that the A-A group represent the major allergies, the N-A's the minor allergies. In presenting this second premise I would say that all persons with the allergic gene manifest symptoms at one time or another, but that those with heterozygous or mixed inheritance are more likely to have minor, evanescent or borderline symptoms. This being the case, according to the above table only 34 per cent of the population could be allergic. But I would again emphasize that the statistical studies have not yet been sufficiently comprehensive for accurate figures, and that in reaching the figure of 34 per cent we have continued to accept the statement that one-third of all allergies develop some allergic symptom prior to puberty.

From Fig. 14 we see that there are seven possible combinations which will produce a genotype NN, seven which will produce AA and ten which will produce NA. If we should assume that the genes N and A occur with equal frequency, we would then find that the NN and the AA combination should

occur in the population 29 per cent each. Forty-two per cent of the population would have the gene N A. Of course, there is no justification for the assumption of equal distribution or incidence of the two genes. But, accepting this as probably the highest incidence of A as compared with N which one might expect, this gives us 71 per cent of the population in which the gene A appears either alone or mixed. This would then mean that upwards of 71 per cent of the population might develop allergy, either major or minor. Assuming that the basic points of Wiener, Zieve and Fries are correct, the truth probably lies somewhere between 34 per cent and 71 per cent, and the correct figure can be determined only following more comprehensive surveys.

I make no brief for my own interpretation as being more logical or tenable than the other. It is an alternative and should be considered. In either interpretation the statement made by Wiener and his associates should be emphasized, to the effect that "the relative frequency of the two genes is not the same in every country and race, since the incidence of allergy varies in different parts of the world just like the incidence of other hereditary characters such as blood groups, eye color, etc.," and that varying environmental conditions will play a part in determining whether or not a patient, especially one with mixed genes, will at some time manifest symptoms.

Conclusions

Summarizing, I feel that until further evidence is presented, we should accept the most logical theory so far presented, to the effect that the inheritance of allergy depends upon the presence of an abnormal or allergic gene; that when two such genes appear in the chromosome frank allergy will develop early in life; that when an allergic gene is combined with a normal or nonallergic gene allergy may develop after puberty or not at all, or in minor form, but the tendency is again transmitted to offspring; and that when no allergic genes are inherited, allergy will not develop.

Allergy in Twins

There has been no great opportunity for the study of allergic responses in twins. Cooke and Vander Veer (1916) reported that among six pairs of twins three pairs showed identical sensitizations. There were two pairs whose mothers were also allergic. One pair showed identical sensitizations with the mother while the other pair manifested dissimilar reactions.

In a discussion of this subject (1937) the following observations were reported.*

In a pair of identical twins, one had severe pollen asthma, the other had no allergic symptoms.

In two pairs of identical twins both had asthma. One set were adults and early allergic history was not noted. The pair of children experienced onset of asthma at ages ten months and eleven months respectively. (Benson.)

In a pair, both with asthma, pollen was the excitant in one, food in the other. (Credille.)

Among several pairs of identical twins studied from birth to seven or eight years in The Brush Foundation in Cleveland, there were several instances in which, during the period of observation, only one of the two developed active allergy. (Cohen.)

*J. Allergy 8: 273, 1937.

In a set of identical twins, eight years old at the time of the report, both had developed asthma at age four following an upper respiratory tract infection. Both reacted by skin test to the same foods, wheat, mustard and radish; and both reacted to ragweed, although they manifested no symptoms of pollinosis. (Fineman.)

In the chapter on Anaphylactic Shock mention will be made of a pair of twins exposed to diphtheria. One had urticaria. The other had had no allergic manifestations. The physician gave prophylactic diphtheria antitoxin, only to the twin without allergic symptoms. This twin promptly died of anaphylactic shock. One should bear in mind that the absence of symptoms does not necessarily indicate the absence of allergy.

CHAPTER XII

GROWTH OF THE ALLERGIC CHILD

Todd and his collaborators have undertaken serial studies of the growth and development of allergic children as compared with normal children. They find that obstruction in the upper respiratory tract due to edema of the nasopharyngeal wall and turbinates results in nasal obstruction, septal deviation and underdevelopment of the sinuses with consequent diminution in vertical growth of the face and its projection forward. This produces a narrow pinched nose and constriction of the upper dental arch, so that there is inadequate space for lodgement of the developing and erupting teeth. The allergic facies results.

They traced fluctuations in weight gain to gastrointestinal allergy. "When gastrointestinal sensitivity is most pronounced, the weight gain is least." Children with winter allergy gain less in winter than in summer, while those with summer allergy gain less in summer than in winter. Allergic children are likely therefore to show seasonal fluctuations in weight which disturb the height-weight ratio.

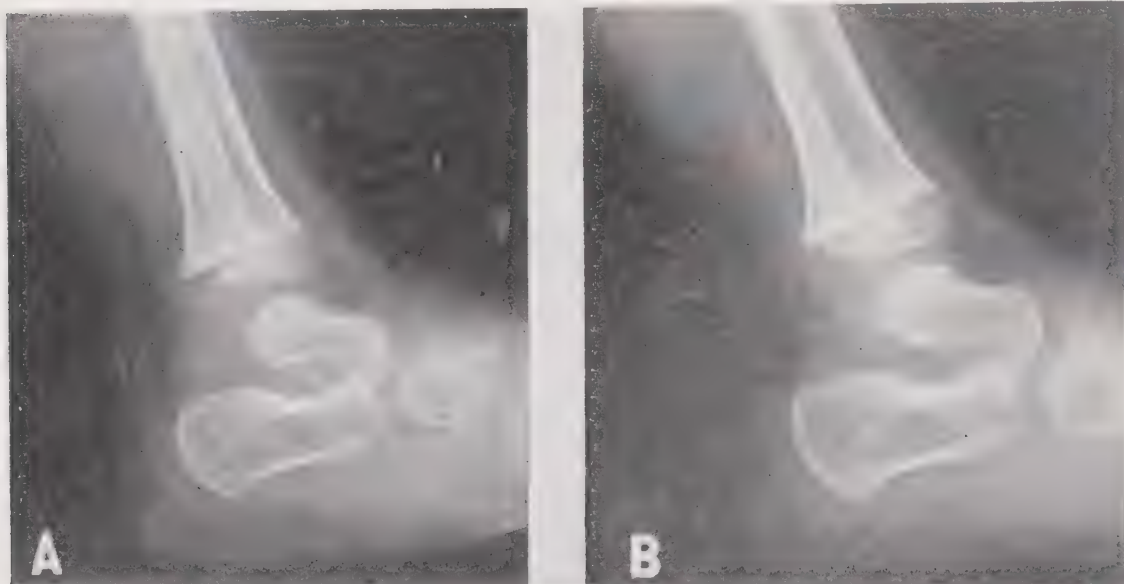


Fig. 15.—Scars and scorings on lower tibia indicative of periods of ill health. Male, white; age, (A) 2 years 0 months, (B) 2 years 6 months. The single white line scar in A is the result of tonsillectomy eight months previously. This appears farther up the shaft in B. A second white line is now present, as a result of measles six months earlier. On the tibial shaft adjoining these scars are finer multiple scorings not very well reproduced in the illustrations but indicative of repeated gastrointestinal disturbances resulting from masked food allergy despite treatment. Contrast, however, the outstanding plainness of the scorings on the tibia of the untreated child in Fig. 16. (From Todd, T. W.: *The Record of Metabolism Imprinted on the Skeleton*, *Am. J. Ortho. and Oral Surg.* 24: 811, 1938.)

Scoring of the teeth due to diminished calcium production during protracted illness such as measles has long been a recognized condition. With the development of the roentgenogram similar scorings or scars in more recently formed bone near the epiphyses of the long bones were recognized. Todd and his coworkers described scorings in these areas, "a watered silk appearance in the growing end of the long bones, particularly the lower end of the tibia," which in allergic children they attribute to nutritional disturbances asso-

ciated with gastrointestinal allergy. They represent periods of diminished growth. "In nonallergic children during the grade school stage, growth proceeds in limbs and trunks in approximately the proportion of 4 to 3. But in children with a pronounced allergic handicap, the proportion of growth in limbs to that in trunks is 2 to 1 or even greater. If the allergy is very severe, growth in stature is also slowed down, and the child is small in stature as well as light in weight." They find that during active episodes of gastrointestinal allergy mineral deposit is slowed. They have even observed a difference in the roentgen picture of the soft tissues and joints which they attribute to subclinical edema.*

Cohen and Friedmar (1937) have suggested utilization of roentgenograms showing scorings as an index of adequate control of gastrointestinal allergy. Children whose bones showed no scoring were not placed on dietary restrictions.



Fig. 16.—Scorings on lower tibia from a child with untreated gastrointestinal allergy. Male, white, aged 4 years 6 months. By contrast of this figure with Fig. 15 the effect of appropriate treatment can be gauged.

In studying both figures it should be recognized that scars and scorings differ fundamentally from textural deviations in bones such as osteochondrosis, rarefaction, "marble bones," and changes in trabecular structure by thinning, fragmentation, beading, or general thickening. The latter group denotes a general metabolic modification of considerable duration, whereas scars and scorings register quite temporary interruptions of growth. Of the two, scars are more apt to be present over a number of years and may even be permanent. Park and Howland described them as transverse lines. Each is produced by a definite clinically evident disturbance in health. Nevertheless, the fact that they originate in a metabolic disturbance of short duration such as the height of a fever, the occurrence of injury, or the constitutional shock of an anesthetic, permits their utilization as calibration lines from which to measure increments of growth, provided they are not so numerous as to imply impediment to the regular velocity of growth.

Scorings are always more numerous and more transitory than scars. They give the impression of watered silk markings. They register minor and usually subclinical disturbances of health. Like scars, they have no diagnostic significance other than disturbed metabolism. But their occurrence in any particular health defect being granted, their fleeting character gives objective evidence of the fluctuations in the progress of that particular disorder. Scorings appear in many illnesses but seem to have a common character of being mediated by gastrointestinal disturbance. When, for example, the allergy is manifested solely in the respiratory passages, scorings do not occur. (Extracted from Todd, T. W.: *The Record of Metabolism Imprinted on the Skeleton*, *Am. J. Ortho. and Oral Surg.* 24: 811, 1938.)

*Two food allergies in the writer's experience remarked that, although formerly their teeth were soft and required frequent dental care, allergic dietary avoidances had been followed by great apparent improvement in the dental condition.

Where scoring occurred the diet was restricted until no new scorings could be seen. As long as new scorings continue to appear food allergy is probably not adequately controlled.

Scorings do not persist indefinitely, disappearing within two years. They are not common after age 6. They are best seen in the lower ends of the tibia and radius. Since these ends grow approximately 9 mm. per year, two to three months should elapse between x-rays, to allow sufficient bone to develop between the growing point and the previous scoring for determination of the presence or absence of new scoring. The longitudinal interval between scorings does not increase. The growing ends of a long bone will move steadily away from two small lead shots implanted in it but the shots themselves will not move with respect to each other. All increase in length takes place at the epiphyseal line. The scoring represents an area of enhanced lime deposit due to temporarily diminished growth.

Although bone scoring occurs in nonallergic children, Cohen and Friedmar conclude that its occurrence in allergic children is sufficiently frequent to be of statistical importance and that, when it does occur, its study may be utilized as a measure of the efficacy of treatment. Chobot and Merrill point out that this roentgen shadow is not diagnostic of allergy, occurring in growing children secondary to starvation, dehydration, acute infections or deficiency disease. They have observed it in a gorilla, not allergic.

Bone scoring is therefore not diagnostic of the allergic state but, when occurring in allergy, may be followed as an index of therapeutic progress.

CHAPTER XIII

MINOR ALLERGY

Although only one-tenth to one-sixteenth of the population has been generally supposed to be allergic, I have long since been impressed by the surprisingly large number of individuals who, in conversation, mention some allergic symptom which they have had at some time in the past. I made the statement at one time that although 7 per cent or possibly slightly more are frankly allergic, if one would also include those individuals who have at some time had some minor allergic manifestation, usually evanescent in character, the frequency of the disease would be found to be more nearly 40 per cent.

Early observations.—Accordingly, in the summer of 1932 I undertook a survey of presumably nonallergic individuals. This was a small group of 100 persons and limited to those who denied being subject to asthma, hay fever, urticaria or eczema. The sampling method consisted in "buttonholing" friends and acquaintances at the dinner table, in the drawing room, on the train or elsewhere, and drawing them into a description of their symptomatology by means of a general discussion of allergy, followed by my own personal experiences.

My personal experiences with allergy served as an excellent starting point because I consider myself an excellent example of minor allergy and because, having described myself it was easy to draw out the subject of investigation, concerning himself. I am not subject to asthma, hay fever, urticaria, eczema or migraine. I have never had any illness of more than a few hours' duration which might be termed allergic. I would certainly be recorded in the average survey of the heredity of allergy as being nonallergic.

CASE HISTORY.—Once or twice each year for several years I had had attacks of diarrhea, of unknown etiology and short duration. I had been unable to determine the cause until, one day on a transcontinental train (therefore with no direct environmental change for several days), shortly after breakfast the malady appeared. The customary breakfast, like that of most Americans, consisted of orange juice, bacon and eggs, toast and coffee. On this morning, however, there had been a change, peaches having been substituted for orange juice. Peaches consequently came under suspicion and in the course of the next several months it was found that diarrhea usually followed the eating of peaches. Curiously, almonds, members of the same botanical group as peaches, also caused the symptom. With the avoidance of almonds and peaches, the symptom disappeared. A year later I could eat peaches without return of trouble.

A year later cherries produced the same symptom. Cherry belongs to the same botanical group. This lasted but for one summer. Prior to and following this particular summer cherries have been eaten with impunity.

During the last three years the same symptom has appeared nearly each time after eating mushrooms. Incidentally, the skin reaction to mushroom is positive.

I am not subject to headaches in any form, but one afternoon after eating shrimp a typical unilateral supraorbital headache occurred. Suspecting shrimp, two days later they were again eaten, but without consequent symptoms. This experiment was repeated two weeks later, again with negative results. Concluding that shrimp was not the cause of the headache, I returned to my customary eating of shrimp. Two or three months later the same headache returned, again after eating shrimp. I eat shrimp frequently. Only rarely do I experience the headache, but never except after having eaten shrimp. As a rule, shrimp may be eaten with impunity but it would appear that occasionally it produces a migrainous type of headache. This, we shall see, is very characteristic of food allergy, that an allergenic food may be eaten at times with impunity, at other times with consequent symptoms. The first one or two dishes of strawberries each season produce hives. Thereafter, no symptoms follow.

On only two occasions has *evipal*, one of the newer synthetic hypnotics, been taken. There was a ten-day interval between the two doses. The second dose was followed within twenty-four hours by a generalized dermatitis which lasted three or four days. No more *evipal* has been taken and there has been no return of the dermatitis.

During the summer I often have occasion to sleep with the blanket turned back over the foot of the bed, with but a sheet for cover. If, during the night, one foot comes in contact with the wool blanket, remaining there for some time, severe itching of the soles may develop, which, if it extends on to the looser area of the dorsum, becomes frank urticaria. This symptom occurs under no other circumstances.

During one summer I had the unhappy experience of developing severe vasomotor rhinitis each time after taking a cocktail made with rye whiskey. Within twenty minutes profuse sneezing and rhinorrhea would ensue which would last for about forty minutes with the drenching of several handkerchiefs. No other alcoholic beverage save that made from rye produced this reaction. This developed only during one summer and has not recurred.

This case has been reported in detail because it was due to interest in my own experiences that I undertook a survey for similar cases, and because it indicates so well what I intend to imply in the term minor allergy. Here is a person who, although not frankly allergic, has had classical allergic symptoms referable to the upper respiratory tract, gastrointestinal tract, the skin and the nervous system. In the skin the symptoms have been both acute and subacute.

Preliminary Survey

The preliminary survey of 100 presumably nonallergic individuals failed to show any history of anything that might be interpreted even as evanescent allergy in 28. In 11 the symptoms were suggestive but not definite enough to be termed positive. Sixty-one had at some time experienced one or another allergic manifestations.

TABLE V. ALLERGIC MANIFESTATIONS AMONG 61 "NONALLERGENICS"

Urticaria	29
Eczema	6
Hay fever	1
Hyperesthetic rhinitis	37
Asthma	3
Sick headaches	15
Indigestion	47

Gastrointestinal symptoms.—By far the commonest symptoms were gastrointestinal, afflicting 47 of the 61 persons. Symptoms mentioned are shown in Table VI. These obviously may be found in association with many types of gastrointestinal pathology other than allergy, but the interesting feature was that

TABLE VI. DIGESTIVE SYMPTOMS ATTRIBUTED TO SPECIFIC FOODS AMONG 47 SO-CALLED NONALLERGENICS

SYMPTOMS	TIMES MENTIONED
Diarrhea	14
Nausea	12
Indigestion	9
Vomiting	8
Continue to taste	7
Cramps	7
Gas	5
Belching	4
Heartburn	4
Palpitation	2
Sore mouth	1
Sour stomach	1

each of the 47 had himself discovered that a specific food was responsible for symptoms and that as long as he avoided that food he was free from the digestive symptom. They had cured themselves by avoiding the offending foods.

A curious symptom mentioned by 7 was that of continuing to taste the presumably allergenic food. There are two reasons for including this in the tabulation. First, I have observed it a not uncommon symptom among frank allergies who give positive skin reactions to the foods that they continue to taste. Second, this was but one of several symptoms, not the sole diagnostic one.

The experience of continuing to taste the flavor of onions or sauerkraut is probably common to most persons. Allergic persons will complain of persistence of the flavor of such foods as fresh cabbage, banana, eggs, Irish potato. The flavor may last twenty-four or forty-eight hours. One is no more justified in designating this symptom allergic than one would be with symptoms such as diarrhea, nausea or vomiting. But when they do occur in an allergic individual, consequent to the eating of an allergenic food and at no other time, they may be considered as part of the allergic picture.

Nasal symptoms.—The next symptom in order of frequency was that of hyperesthetic rhinitis, described by 37. Another had had typical seasonal hay fever in childhood which had disappeared spontaneously. A normal person cannot successfully sneeze six times with no longer interval between sneezes than is required to take a deep breath. This is characteristic of hyperesthetic rhinitis. Undoubtedly most hyperesthetic rhinitis is allergic. A point of special interest in this group, as brought out in Table VII, is that with only three exceptions each could name the substance or situation which would initiate sneezing barrages.

TABLE VII. CAUSES OF SNEEZING AMONG 37 NONALLERGICS

CAUSE	TIMES RECORDED
Getting out of bed	6
Sudden chilling	4
Wind	4
Intense sunlight	4
Dust	6
Soap powders	4
Drinking whiskey	2
Beer	1
Pollen	2
Taking aspirin	1
Eating chocolate	1
Perfumes	1
Tobacco smoke	1
Mold	1
Odor of fresh paint	1
Cause unknown	3

Urticaria.—Twenty-nine had urticaria. Histories such as the following are illustrative:

Aged 37, had had hives for one summer at age 5, cause unknown.

Aged 57, had had hives at age 15 and again at 42, cause unknown.

Aged 44, hives between ages 30 and 32, due to tomatoes. He has since eaten tomatoes as often as twice daily with impunity.

Aged 42, hives and diarrhea at 32, due to raspberries and strawberries. Can eat them now.

Here again the majority knew the cause. They were recorded as follows: unknown 11, strawberries 9, tomatoes 8, chocolate 2, with one each for ice tea, peach, raspberry, banana, cheese, milk, potato, walnut, lobster, salt herring, pork, beer, coffee and palmolive soap.

Asthma.—Six had asthma, 4 in childhood, cause unknown; one at age 25 due to pork, fruit and banana; and one in early adult life from tomatoes.

Three, aged 23, 38 and 44, had had asthma at ages 15, 16 and in childhood. None knew the cause.

Headache. Thirty two had occasional or recurrent or chronic headaches. Fifteen had found from their own experience that specific foods caused headaches and had relieved themselves through avoidance.

Contact.—There were 14 examples of contact allergy or irritation. Of these, wool was responsible for 9, soap for 2, rayon, hollyhock and weeds for 1 each.

In the entire series of 61 there was evidence of food allergy in 46, inhalant allergy in 38, contact allergy in 14, physical allergy in 9, and allergy to drugs in 5.

Type of allergen. The victims of hyperesthetic rhinitis and urticaria could usually name the causative factor. This held equally true among the instances of food allergy. Foods responsible for indigestion in this series were in order of frequency, cucumbers, watermelon, onion, cabbage, strawberry, pork, tomato, apple, banana, pepper, turnip, raspberry, corn, veal, sardine and a scattering of other foods with occasional mention, including cauliflower, almond, cherry, peanut, pineapple, Roquefort cheese and huckleberry.

It should be noted that almost without exception these are foods eaten only occasionally. The situation is altogether different from that observed in the study of frank allergic invalidism, in which the most frequent offenders are the foods most commonly eaten, including wheat, egg, milk, peas, beans, etc. The minor allergic is sensitized to substances with which as a rule he comes into only occasional or intermittent contact. In this series, wheat, egg, beef, chicken, peas, coffee and tea were not mentioned at all; milk, potatoes and beans but once each.

We see a similar situation in the 15 with recurrent headache, where foods mentioned were peppers, cabbage, chocolate, peanuts, cauliflower, onion, cheese, watermelon and candies. One was allergic to egg. Among those with skin rash, strawberry and tomato easily headed the list.

Occasional contact substances. The inference to me is obvious that this group of mild or borderline allergies differs from the frank or more chronic allergies chiefly in the fact that they were fortunate enough to become sensitized to allergens with which they had only occasional contact. As a consequence they were easily recognized and subsequently avoided. The frank allergic, unable to recognize the offending allergen, remained in contact until his allergic state became firmly established.

Transient sensitization. Another interesting observation developed from this study of 100 presumably nonallergic individuals. Not only were the excitants *occasional allergens* but there was evidence of a tendency to loss of sensitization such as I have described above in my own case. Sensitization once developed is not necessarily permanent. The following examples indicate the temporary or evanescent character of sensitization.

Mr. H. experienced hives after eating tomatoes during the World War and for two years thereafter. Since then he has eaten them usually about twice daily without reaction.

Miss R., aged fifteen, had had hives at ten for two months, attributed to strawberries. She avoided them for a time but can eat them now without difficulty.

Mr. R. experienced urticaria from strawberries in childhood. He eats them now without discomfort.

Mrs. B. found that during one summer watermelon consistently produced vomiting and diarrhea, but since then, she has had no trouble therefrom.

Mrs. F. eight years ago found that watermelon produced angioneurotic edema of the hands and tongue. Even the juice on the hands produced swelling. Watermelon now causes no symptoms.

Miss W. observed that several years ago strawberries caused abdominal cramps and nausea. She avoided them for several years and this year has eaten them without discomfort.

Mrs. M. had hives in the summer time three years ago, cause unexplained. Since then there has been no return.

Mrs. C. experienced eczema in childhood, involving the hands only and lasting for three months. This was presumably due to chocolate. She has had no return of trouble until within the last few months when the eating of chocolate produced urticaria and cardiac palpitation, often with headaches. Plums consistently produced diarrhea a year ago; none before or since.

Mrs. B. experienced diarrhea from corn in childhood. She now eats corn without difficulty.

Mr. G. several years ago regularly had sour stomach and heartburn from cucumbers. He now eats them without symptoms.

Tuckwiller,* on the contrary, had a man who developed hay fever in the ragweed season at age 9 months and had it every year thereafter at the same season for 49 years. He was then found sensitized to ragweed and received ragweed hyposensitization for four years. Results were very good each year. He died at age 53 from heart trouble. This may well be the longest case of ragweed pollinosis on record. Some persons consistently maintain sensitization to the same allergen.

This is particularly true of the pollen sensitizations. Others, usually those sensitive to foods, often change their sensitizations. This is not true of the occasional food-sensitive person who has a very intense reaction to a certain food. These seem to maintain their sensitiveness to the same food throughout their life even though the food may be scrupulously avoided. Those less sensitive may change their sensitization and retesting is indicated when recurrence of symptoms suggests the development of new sensitizations.

TABLE VIII. SURVEY OF ALLERGENIC FOODS

	POSITIVE REACTORS IN MAJOR ALLERGY PER CENT	FOODS BLAMED IN MINOR ALLERGY
Wheat	24.0	0
Milk	14.0	1
Kidney Bean	12.0	2
Egg	9.5	1
Potato	9.5	0
Celery	8.0	0
Coffee	7.0	0
Cherry	7.5	1
Eggplant	7.0	0
Prune	7.0	1
Tomato	7.0	10
Cabbage	5.0	8
Onion	6.5	9
Cucumber	2.5	13
Strawberry	.1	10
Watermelon	0.0	13

Table VIII indicates the foods found, by skin testing, to be responsible for the major portion of the major allergy and, in the second column, those incriminated most frequently in the minor allergies. It is obvious that major allergies are due to the substances with which the patient is in frequent contact while minor allergies are due most often to those with which there is only occasional contact.

These allergic episodes are termed "minor allergies" because they are of minor importance. They occur only occasionally or only at certain times in the life of the individual. They might well be designated as "transient allergies"

*Tuckwiller, P. A., Charleston, W. Va. Personal Communication.

since many of them fall into the groups of asthma, hay fever, urticaria, and allergic rhinitis, which usually are designated as major allergies. Since these "minor" allergic manifestations are due to foods or other substances which are met with only occasionally, they usually are recognized and avoided and, after sufficient avoidance, the sensitiveness usually is lost. In every other respect it would appear that they are entirely comparable to the "major" allergies.

Tendency to spontaneous recovery.—The transient allergic rarely needs advice or study by the physician. He realizes the etiology of his symptoms, curing himself by avoidance. I find evidence that the normal physiologic tendency is toward gradual loss of specific sensitization. There has been an impression that once one becomes sensitized, specific sensitization tends to persist through life. But students of allergy have in the last few years had the opportunity of watching sensitizations appear and disappear, to be replaced by new ones. Likewise, serial skin retesting will show that foods and other allergens, once positive, may become negative, while others formerly negative become positive. It is but a simple step to postulate that the natural tendency of specific sensitization is toward gradual disappearance. The rapidity of disappearance depends upon the degree of intensity of the sensitization and upon whether the reaction is kept active by repeated or continued contact with the allergen. If avoidance of contact could be carried out sufficiently long with every allergen, the probability is that sensitizations would eventually disappear. New ones of course may take their place. Allergists, for example, have found that food allergy may be successfully handled through avoidance, often with actual cure. Prolonged contact intensifies the allergic reaction and delays recovery.

Not all persons lose their sensitizations after a period of avoidance. Not a few report reappearance of symptoms each time they eat the offending food. Even when sensitization disappears, avoidance must be rather prolonged. In a series of migraine cases I found that on the average four and one-half years must elapse following the inception of avoidance until loss of sensitization is complete. Some still continued reactive at the end of twelve years, although we cannot be certain that they completely avoided the food during the entire interval.

The same would probably be true in inhalant allergy, if one could avoid the excitants sufficiently long. Exposure to pollens is intermittent but it is annual, and it is rare for one to avoid the pollen excitant for an average of four and a half years.

A Community Survey

Having established the probable trend in this preliminary series, we proceeded to a larger survey involving all persons allergic and nonallergic in an entire community with enough additional persons in the neighboring territory to make a total of approximately 500. The nucleus for this survey was the village of Clover, in southern Virginia, with a village population of 251. The total included in the survey was 508. The information was obtained by Miss Virginia Gregory, a trained social investigator, who carried out her part of the work independently of my own previous study.

Among the 508, fifty-five, or 10.8 per cent, were promptly recognized as victims of frank or major allergy. They had either asthma, hay fever, urticaria, recurrent headaches or indigestion for which specific foods were known to be responsible. A history of frank asthma or seasonal hay fever in the past even though there had been none within recent years also placed a person in this category.

Forty-eight and one-tenth per cent presented evidence of minor allergic manifestations at one time or another in the past history; 31.3 per cent gave no such history; the remaining 50, or 9.8 per cent, were questionable as far as their records could be analyzed and are, therefore, placed in the nonallergic group.

TABLE IX. DISTRIBUTION OF SYMPTOMS AMONG 55 MAJOR ALLERGICS IN A COMMUNITY OF 508 PERSONS

SYMPTOMS	CASES	PER CENT OF ALLERGICS	PER CENT OF POPULATION
Hay fever	27	49	5.3
Urticaria	25	45	4.9
Gastrointestinal	22	40	4.3
Asthma	17	31	3.3
Migraine	16	29	3.1
Vasomotor rhinitis	15	27	2.9
Eczema	3	5	0.6
Angioneurotic edema	2	4	0.4

An analysis of the series brings out interesting facts. Of those major and minor allergies who attributed symptoms to definite causes, 62.6 per cent responded to foods, 23 per cent to inhalants, and 14.4 per cent to contact allergens. Of the same group 50.7 per cent manifested gastrointestinal symptoms, 47.2 per cent skin lesions, 26.4 per cent nasal symptoms, 9 per cent migraine or recurrent headaches, 6.2 per cent asthma; and there were a few cases of less definite symptomatology, such as recurrent sores in the mouth, recurrent so-called conjunctivitis, and recurrent kidney colic.

Foods.—Table X records the offending foods designated by the 244 minor allergies in this survey together with the symptoms produced. Here again the infrequency with which symptoms are attributed to staple foods such as wheat, milk, egg, beef and coffee is noteworthy.

The symptoms described are of great variety and might be attributed to various organic gastrointestinal lesions, but the point which should be emphasized and which justifies the conclusion of an allergic etiology is that the patient himself finds that only a single food or a few certain foods produce the symptoms and that he can eat others with impunity. These are cases of food idiosyncrasy. The first eight columns bring out that symptoms may be referable to the upper intestinal tract or the lower intestinal tract as is the case in frank allergy. The next four represent the skin and central nervous system, tissues often involved in frank allergy. The last three columns, chest pains, choking, and the phenomenon of continuing to taste the food for twenty-four hours or more after it is eaten, are included, first, because they are symptoms actually described by the patient, and second, because the foods incriminated correspond so closely to those chiefly incriminated in the preceding columns that one is tempted to wonder whether allergy is actually responsible for these symptoms.

A few other miscellaneous symptoms were attributed by the patients to food idiosyncrasy. Ulcers in the mouth were attributed one time each to strawberry, peach, cantaloupe, chicken, sea foods and four times to tomato. Recurrent typical gallbladder attacks were attributed once each to blackeye peas, Irish potato, beef and oyster. One patient experienced backache each time she ate strawberries. One patient complained of blurring of the vision after eating apples. One had vertigo from watermelon, one sleeplessness each time she ate tomatoes. Eczema was attributed once each to cherry, peanut and cheese and twice each to strawberry, tomatoes and lamb.

The phenomenon of continuing to taste the food for many hours after it has been eaten bears closer study. It is such an indefinite symptom and so frequently mentioned in clinical medicine that one would be inclined to doubt any allergic connection. It was mentioned as a complaint 109 times. Only 10 times was it the only symptom. Ninety-nine times it was mentioned in connection with some other allergic manifestation.

TABLE X—CONT'D

FOODS	NALSEA	VOMIT- ING	HEART BURN*	BELCH- ING	GAS	CRAMPS	COLITIS	DAR- RHEA	HIVES	ITCHING	RASH	HEAD- ACHE	CHEST PAINS	CHOK- ING	TASTE	TOTAL
TIMES MENTIONED																
Cornmeal	1	1		1		1						1			1	5
Pineapple																1
Corn	14	11	7	13	3	13	2				1	13	1	3	24	104
Molasses																1
Beef	1		1	1	2	2	1		1				1	3	4	14
Veal	1		1	2	1	1	1							1		7
Milk	1		1		1							2			1	8
Buttermilk			1													6
Cheese	2	1	1	1	1	2	1						1	1	1	1
Egg	3	2	1	1	1				2				1	1	1	11
Chicken		1	1						4				1		2	13
Pork		1	4	1	2	5						3	1			2
Pean			1													23
Ham	1		2			3				1					1	1
Lamb					1	2	1						2		1	5
"Sea foods"	3	4	4	1	1										1	15
Crab	3	2													1	3
Herb	1	1				1									1	3
Lobster	2	1		1											2	4
Oyster	2			1	1	1										5
Sardine									1							1
Soup	1															1
Miscellaneous																
Bouillabaisse	3	1		1		1		1				1				8
Fruit			1													1
Ice cream						1	1									2
Layer	1		1				1				1					4
Pie								1								1
Sweets		1	1													2
Salad greens			1				1								1	4
Sausage	1	1														4
Mayonnaise	3		2	2				1			1					7

*Heartburn—“Sour Stomach—Acid Stomach.”

Another interesting observation is the great variety of foods which may be responsible for symptoms. Almost every food is mentioned one or more times. This has a practical application in connection with major allergy and the so-called elimination diet. Those who would dispense with the preliminary sensitization test and start the patient on an elimination diet fail to realize that the frank allergic, in addition to being more often sensitized to staples, is at the same time sensitized to occasionals, and probably in the same frequency as the minor allergic. But he is less able to discover the offending occasionals because of his more or less persistent symptoms from the staples. It is therefore not enough just to prohibit those foods which from experience have been found to be frequently allergenic. Most major allergies will at the same time require the prohibition of certain occasional foods to which they are sensitized. Unnecessary delay may therefore be avoided by the preliminary application of sensitization tests and the prescription of a strictly individualized trial diet based upon the findings.

Inhalants.—Inhalant allergy is also represented in this series of minor allergies. Obviously the individual is less often able to ascribe his symptoms to a specific etiologic inhalant factor. The chief inhalant manifestation was explosions or barrages of sneezing. Some could only state that these periods of sneezing occurred only under certain circumstances or in certain environments, such as "while playing golf in the spring," or "out of doors," or "when frying food." But it is surprising to observe how often a definite cause could be cited.

TABLE XI. SUBSTANCES RESPONSIBLE FOR RESPIRATORY SYMPTOMS IN MINOR ALLERGICS

SUBSTANCE	TIMES MENTIONED	SUBSTANCE	TIMES MENTIONED
Dust	53	Marigold	1
House dust	12	Roses	1
Dust outdoors	2	Soap flakes	5
Hay dust	3	Soaps	3
Tobacco dust	3	Shaving soap	1
Threshing grain	1	Washing powder	5
Smoke	1	Orris root	1
Tobacco smoke	1	Crowds	2
Coal gas	1	Wheat flour	1
Ragweed	6	Feathers	1
Weeds	4	Flax	1
Grasses	7	Frying food	1
Pollen	6	Cocoa butter	1
Oak	1	Strong light	10
Flowers	1	Heat	1
		Wind	1

Dermal.—Foods responsible for dermal manifestations are indicated in Table X. Atropine was responsible in one case of hives; quinine in one caused attacks of angioneurotic edema. Table XII indicates other substances accused as responsible for dermal manifestations, presumably acting chiefly as contact allergens. Contact with wool is of special interest. Forty-one of the allergic series complained of itching, rash, or hives from contact with wool. Eleven of the questionable cases and 1 of those classed as nonallergic did likewise. Seventy-seven and three-tenths per cent of those complaining of symptoms due to wool were classed as allergic on the basis of related symptoms. Thirteen and seven-tenths per cent of all the allergic cases complained of symptoms due to contact with wool, while only 2 per cent of the nonallergics did so.

Criticism.—The criticism might properly be raised that in this series there may have been a tendency to include as allergic, manifestations which might have been due to other causes. In isolated instances this is entirely possible, but I believe that the error due to this factor is small, since in such a very large proportion the individual has been able to incriminate definite specific substances. There is an additional way in which the accuracy of the survey may be assayed. Allergy may be and often is limited to one system such as the gastrointestinal, the respiratory tract or the skin. But it also often involves more than one system. When two or more systems are involved, there is, then, even less doubt concerning the allergic nature of the symptoms. In this series of 244 minor allergies (Table XIII) one system alone was involved in 144, while two or more systems were affected in 130 cases. In 164, symptoms were attributed to one variety of allergen, food, inhalant or contactant, but in an additional 80 two or more types of allergens were incriminated. The multiple etiology and polymorphous

response observed in this series occur in about the frequency that we would anticipate from our knowledge of major allergy and confirms the conclusions that the statistics are reliable.

It is possible that a survey based upon an exhaustive personal discussion with each patient, together with the indicated sensitization studies, might show a lower percentage with minor allergy, but I do not anticipate that the difference from our findings would be sufficient

TABLE XII. CONTACT SUBSTANCES RESPONSIBLE FOR DERMAL MANIFESTATIONS IN MINOR ALLERGICS

SUBSTANCE	SYMPTOM				
	ITCHING	HAIR	RASH	ANGIO-NEUROTIC	
				ECZEMA	EDEMA (SWELLING)
	<i>Times Mentioned by Patients</i>				
Wheat flour			1		
Wheat		2			
Barley flour	1				
Rice powder			1		
Corn shucks and stalks		10			
Corn fodder		1			
Straw		1			
Hay	1				
Oats	1	2			
Grasses	1		1	1	
Weeds	2	2	3	3	
Scrub oak	1				
Grapevines	4	5	2	1	
Fuzzy vines		1	2		
Zinnia		1			
"Snow on mountain"	2				
Peach skin	1	1			
Vegetable skins	1				
Soaps and soap powders		1	6	1	
Talcum	1			1	
Face powders					
After bath	1				
Wool	27	5	9		
Rabbit hair					1
Rayon	4				
Cause unknown		13		2	

TABLE XIII

SYSTEMS INVOLVED	TIMES MENTIONED
Gastrointestinal, only	49
Upper respiratory, only	12
Skin, only	35
Nervous, only (headaches)	2
Gastrointestinal and upper respiratory	22
Gastrointestinal and skin	24
Gastrointestinal and nervous (headaches)	14
Gastrointestinal, nervous and respiratory	6
Gastrointestinal and lower respiratory	1
Skin and nervous (headaches)	10
Skin, respiratory and gastrointestinal	17
Skin, nervous and gastrointestinal	10
Skin and upper respiratory	15
Respiratory and nervous (headaches)	1
Renal	1
ALLERGENS RESPONSIBLE	
Foods only	103
Inhalants only	11
Contactants only	4
Foods and inhalants	20
Foods and contactants	14
Foods, inhalants and contactants	1
Inhalants and contactants	1

to invalidate our conclusions. I recognize the hazard involved in attempting to designate as allergic, recurrent headaches and dermatitis, from the patient's general description, but would once again emphasize the importance in this connection, of the patient's ability usually definitely to name the offending agent.

Observations by Other Investigators

The conception that over half of the population in the area studied and possibly elsewhere has or has had some form of allergy, is new. Only one entirely comparable survey has since been made, that of Pipes. However, other investigators have reported observations which point in the same general direction.

Walzer, in discussing the unreliability of a negative allergic history among relatives of an allergic patient, writes:

"It is surprising to find how often these supposedly normal individuals give marked reactions to various atopens. These cannot always be confirmed by a clinical history of sensitivity in the subject any more than the positive reactions on the direct testing of patients are always proved to be clinically significant. But definite instances occur in which a pointed question as to the result of the ingestion of food, to which the supposedly normal parent gives a marked reaction, elicits the information that the subject usually avoids it. Either he has an inherent distaste for it or it gives him unpleasant symptoms as 'heartburn' or 'indigestion,' or makes him uncomfortable in other respects. In the case of marked reactions to inhalants, the subject will occasionally admit excessive sneezing or coughing following exposure to the substance. Yet in many of these instances, the history of sensitivity has been previously denied by these individuals, nor is it easy to convince them, even in the face of the positive skin reaction, that they are actually hypersensitive. Many of these persons with marked positive reactions and negative clinical histories are probably only potentially sensitive and may develop their clinical atopic manifestations at a later date."

In Chapter IX, I mentioned the observations of Rowe who found that 35 per cent of 400 college students and nurses gave personal history of probable allergy, 31 per cent suspecting foods as etiologic factors. Also the report by Jimenez based on nearly 7,000 interrogatories, to the effect that 35 per cent clearly belong in the allergic group and that an additional 20 per cent are potential allergies.

On the objective side we have Harkavy's report of 30 per cent positive skin reactions in a group of 200 presumably nonallergic patients, following testing with only four allergens, and those of Rackemann and Simon who found that 50 per cent of 60 presumably nonallergic persons reacted positively to one or more of eight test allergens.

Grow and Herman tested 150 normal subjects with 13 extracts: ragweed, timothy, cat dander, dog dander, horse dander, orris root, mixed feathers, wheat, egg, milk, orange, celery and lobster. They observed positive endermal reactions in 55.5 per cent. Forty of the total number gave history of low-grade allergic manifestations at some time in the past but none had had asthma or hay fever. There was no noteworthy difference in the incidence of positive reactions in these 40 as contrasted with those with no history of past allergic symptoms.

Multiple positive reactions were the rule, with an average of 2.65 reactions per person among those with past allergic history and 2.24 in the nonallergic group.

Survey by Pipes.—Pipes has reported a population survey which is directly comparable to my own. His survey includes 700 individuals, residents in and about Jackson, Louisiana, and secondary school children and summer students in the State University at Baton Rouge.

Pipes found the incidence of major allergy in this group to be 13.6 per cent, of minor allergy, 35.8 per cent, making a total allergic population of ap-

proximately 50 per cent. It is interesting that 8 per cent suffered from hay fever. These were all major allergies. Scheppegegrell's original estimate of 1 per cent hay fever in the population was based on questionnaires sent to the physicians of Louisiana. As is well known, the latter is a statistical procedure subject to great error. The careful survey by Pipes in the same state showing eight times Scheppegegrell's estimated incidence well illustrates this point.

Pipes found symptoms among major allergies, with case incidence as follows: hay fever 59 times, asthma 39, migraine 25, urticaria 30, eczema 10, angioneurotic edema 1, colitis 1. Among the minor allergies the incidence is as follows: indigestion 108, urticaria 46, eczema 46, migraine 14, hay fever 5, asthma 3, colitis 1, angioneurotic edema 1.

TABLE XIV. (PIPES' SURVEY)

FOOD	TIMES INCRIMINATED	FOOD	TIMES INCRIMINATED
Cabbage	18	Cauliflower	3
Onion	17	Cream in coffee	2
Melon	15	Sweet potato	2
Banana	9	Oyster	2
Pork	9	Pickle	2
Beef	7	Mandarin	2
Fat	6	Salmon	2
Peanuts	6	Coffee	2
Cucumber	6	Chocolate	2
Sweets	6	Pineapple	2
Tomato	5	Cane syrup	2
Egg	5	Peach	2
Radish	5	Okra	2
Sweet milk	5	Beet	1
Apple	5	Lamb	1
Butter bean	4	English pea	1
Sardine	4	Cocoanut	1
Cheese	4	Celery	1
Fish	4	Collards	1
Bell pepper	3	Apricot	1
Turnip	3	Black pepper	1
Corn	3	Marshmallow	1
Spinach	3	Cream	1
Strawberry	3		

"In every case of minor allergy the sufferer was able to point out a definite causative factor or definite causative factors, whether ingestants, inhalants or contactants. He could thus relieve his allergy by conscious avoidance of a known substance. Foods mentioned by cases with indigestion are shown in Table XIV. Allergenic foods mentioned by minor allergies with symptoms other than indigestion included, in order of frequency, strawberry, tomato, watermelon, banana, chocolate, pork, beet, peach, shrimp, orange, butter, cream, milk, fig, lemon, cheese, sugar, egg, cottage cheese, mackerel, crab, oyster, coffee, Coca-Cola, and onion. Drugs mentioned were quinine, aspirin and calomel. Inhalants were chalk dust, house dust, cow feed and face powder. Contactants were wool, peach down and dried pea."

Significance of Minor Allergy

We may term the minor allergic the *fortunate* allergic. He was so fortunate as to become sensitized to something with which he establishes only occasional contact. For this reason his symptoms are intermittent and he is able readily to recognize a cause and effect relationship between the allergenic substance and his symptoms. He thereafter avoids the offender, thereby curing himself. The major allergic may be termed the *unfortunate* allergic. He is so unfortunate as to have become sensitized to something with which

he is in chronic contact and which he therefore cannot recognize as being the etiologic agent. Examples are found in the staple foods such as wheat, egg, milk, Irish potato, coffee, beef, etc.; in inhalants such a house dust, feathers, orris root, pyrethrum, tobacco; and in invisible seasonal factors such as pollen. In this latter case the contact although intermittent is chronic through the duration of symptoms.

So far as we know it is purely a matter of luck as to whether one will become sensitized to a frequent or occasional contact substance, although there is evidence suggesting that the chemical nature of the allergen, the degree or length of exposure thereto, and inherited predisposition may exert some directing influence.

It should not be understood that the major allergic becomes sensitized only to those substances to which he has constant or prolonged exposure. He also experiences symptoms from the occasional allergen. Patients with major allergy give positive skin reactions both to staples and to occasionals such as cucumber, onion, tomato, cantaloupe, buckwheat, barley, etc. I suspect that if skin tests were made on major and minor allergies using the same series of allergens, it would be found that the major allergic reacts in approximately the same frequency to occasional substances as does the minor allergic. The difference lies in the fact that, in addition, he reacts to the frequent exposure substances.

In this connection Pipes makes an interesting observation. Among the 95 with major allergy, etiologic factors were recognized 41 times. Not infrequently the same factor was mentioned by more than one. Consequently a total of 21 factors were mentioned 41 times. These were strawberries, quinine, cabbage, watermelon, cantaloupe, beef, bacon, aspirin, tomato, pecan, coconut, walnut, peanut, celery, dust, pollen, feathers, chalk dust, face powder, cotton, and smoke from boiling rice. It will be noted that with few exceptions these are substances with which the average person comes into only occasional contact. They are the class of substances incriminated by the minor rather than the major allergic. The interesting feature is that "none of these factors will be noted as playing a major causative role but simply listed as bringing about more trouble." They were not the basic cause but represented additional incidental or occasional sensitizations comparable to those of minor allergies. These major allergies, like the minor, recognized them as offending substances, but were unable to relieve themselves by avoidance, because of additional sensitizations which they could not recognize.

Summary

Upward of 10 per cent of the population develop major allergic manifestations, usually subacute or chronic in character. Approximately 50 per cent give a history of minor episodic manifestations.

The latter are usually sensitized to allergens with which they come into only occasional contact, while the former, in addition, are sensitized to staple allergens with which they come into frequent, often daily, contact.

The difference between the two groups depends chiefly upon the degree and frequency of contact with the offending allergen. Recognition of the allergen depends upon this and determines into which class the individual will fall.

The natural tendency of the allergic state is toward recovery or loss of sensitization provided avoidance of contact is continued through a sufficiently long period.

PART III

THE PHYSIOLOGY OF ALLERGY

The result of shaking a stick at a dog depends less on that gesture than on the condition of the animal at the moment. What is true of the dog is true of the human being. The impact of a stimulus may be far less significant than the condition of the organism which receives the stimulus. Certainly this is true in allergy. Hence, consideration of the constitution becomes of the greatest importance.

—T. WINGATE TODD

CHAPTER XIV

THE PHYSIOLOGY OF PROTEIN DIGESTION

Studies of gastrointestinal absorption, in the production of experimental anaphylaxis, have necessitated a thorough revision of our understanding of the physiology of digestion. No longer can we state that proteins are completely broken down into their constituent amino acids in the intestines, and absorbed through the mucosa as such.

Assuming that sensitization may occur through intestinal absorption, how does it happen? Schloss and Worthen (1926) found by precipitin and anaphylactic tests applied to the urine, that the intestinal tract of normal infants is impermeable to undigested foreign protein. In the presence of gastrointestinal disturbances, however, protein was found to be absorbed, either undigested or partially digested, and excreted in the urine. This seemed a simple explanation. We become sensitized to food protein as a result of gastrointestinal disturbances which allow the passage of undigested allergen into the blood.

Hettwer and Kriz (1925) substantiated these findings by sensitizing guinea pigs to horse serum following its introduction into a temporarily ligated loop of small intestine. They found that stasis and increased intra-intestinal pressure were necessary to promote absorption. They obtained similar results following chemical irritation without stasis, by the introduction of horse serum into the unligated intestine together with small amounts of sodium fluoride. Not only did they sensitize guinea pigs in this manner but using the same method they were able to produce anaphylactic reaction in previously sensitized pigs.

The liver appears to exert a regulatory and detoxicating function during digestion. We have been taught that it removes undigested protein from the portal blood thereby preventing its entrance into the systemic circula-

tion. Egg white injected into the circulation appears in the urine sooner when introduced through an ear vein than through a mesenteric vessel. When injected into a mesenteric vessel, it appears to be removed in part at least by the liver and makes its appearance in the bile. In guinea pigs, previously sensitized against egg white, this protein causes death more rapidly and in smaller doses when injected directly into the systemic circulation than when introduced into the portal system.

Had investigations stopped at this point the current teachings of physiology would have required no alteration. Proteins are digested in the lumen of the gut and absorbed as amino acids except in the presence of local gastrointestinal disturbance, with resulting increased permeability, when they may be absorbed incompletely digested and produce sensitization.

But Rosenau and Anderson (1909) succeeded in sensitizing guinea pigs following the *oral* administration of horse serum as did also Hettwer and Kriz. Victor Vaughan (1910) found that young rabbits could easily be sensitized with milk by mouth or by rectum; "In our work we have observed that hungry rabbits will eat milk when mixed with other foods and seldom are sensitized, but when the milk is introduced into the stomach of a fasting rabbit through a tube, or injected into the rectum, the milk can soon be detected in the heart's blood, and the animal becomes sensitized."

LaRoche, Richet, and Saint Girons (1914) succeeded in sensitizing guinea pigs to egg white by the oral route. Stokvis (1864) as well as Van Alstyne (1913) showed that raw egg white taken into the alimentary tract may enter the circulation and be excreted through the urine. Finally, Walzer and his collaborators (1928) demonstrated by passive transfer that undigested proteins are absorbed and appear in the circulation of normal nonallergic individuals. A small amount of serum from an individual allergic to egg was introduced into the skin of a nonallergic person. When subsequently the latter ate eggs, a local positive allergic reaction appeared at the site of the endermal inoculation. The egg in the food was absorbed and carried through the blood to the site of the inoculation, its chemical makeup still sufficiently characteristic of egg white to give a specific response. This was demonstrated repeatedly not only with egg protein but also with fish protein.

Rosenzweig and Walzer, using the technic devised by Walzer for demonstrating absorption of unaltered protein from the gastrointestinal tract, have shown that allergen absorption from the uterine cervix is a normal phenomenon, being demonstrable in passively sensitized skin sites within from 9 to 25 minutes. Absorption from the vagina occurred in about one-third of the tests, the time being from 40 minutes to 2 hours.

Straus and Walzer (1938) have found that the monkey may be used for demonstrating the absorption of undigested protein. Monkey's skin was passively sensitized with human reactive serum. The allergenic food was fed to the monkey, after which the skin site became positive.

Ratner and Gruehl found that both mature and young animals could be sensitized and shocked by the oral administration of protein foods. Results were obtained in as high as 50 per cent of experiments. They offer these observations as evidence that unsplit proteins pass the intact intestinal wall under normal conditions. Their experiments were carried out under physiologic conditions. They suggest that such normal absorption of protein might serve a useful purpose in maintaining the body in a state of constant immunization against proteins habitually taken in the diet.

Coca (1930) has shown that contrary to former belief, protein does pass in minute amounts through dialyzing membranes. If we consider the alimentary tract such a membrane, he has shown that amounts of food protein sufficient to be of clinical significance may thus pass normally into the circulation. This observation explains those of Walzer and his collaborators.

So we must modify our concept, to recognize that unaltered protein or only partially digested protein may normally be absorbed into the circulation. This does not clarify the question as to why some persons become sensitized while others do not, but it removes the site of initiation of sensitization from the intestinal mucosa to the tissues themselves. The localization of the allergic response in different organs or tissues remains unexplained.

CHAPTER XV

THE MECHANISM AND SIGNIFICANCE OF THE ALLERGIC RESPONSE

As a preface to this phase of the discussion I should state that the conception outlined in this chapter is the writer's hypothesis as published in 1936, concerning which neither approval nor disapproval has as yet been offered by others. The reader should not infer that the views expressed are those generally accepted by students of the subject.

As we have seen in earlier chapters, many theories have been presented to explain the mechanism of anaphylaxis. None has been found so completely satisfactory as to refute all criticism or to explain all of the phenomena. And yet these theories, although unsatisfactory in many ways and later proved for the most part untenable, have been responsible in great measure for our progress. After all, a theory is but a stepping stone in the advance toward knowledge, a point of support which is helpful for the moment but no longer needed after we have advanced beyond it. Without it, advancement would have been more difficult.

Early in experimental anaphylaxis theories appeared thick and fast. Within the last decade or more very few new ones have been advanced. This has been due in part to the fact that the application of Ehrlich's side-chain theory of immunity to anaphylaxis has so nearly filled the need for a rationalization, and in part that our ideas have tended to become fixed in the groove of the side-chain theory, making it difficult to readjust to any different theory. Manwaring has written of the deficiencies in the side-chain theory and has suggested that it would be well to lay aside for future reference the entire schema of immunology based on the specific receptor hypothesis, to start at the beginning in an attempt to unravel the mystery of the origin and nature of antibodies.

However, until a better has been presented, we must continue for practical purposes to utilize this theory, which appears to explain the phenomena more adequately than others.

In his recent hypothesis of the H-substance, Thomas Lewis further clarifies the subject since he enables us to comprehend a possible source of anaphylactic poison in a substance normally present in tissues, one which in toxic doses produces symptoms almost indistinguishable from those of anaphylactic shock. The theory of the H-substance may be adjusted to the tenets of the side-chain theory or may be held independently of the latter, even being adapted to other entirely different theories. In other words, it explains another phase of the reaction. Granted that an antigen-antibody combination, occurring when the antibodies are still attached to the living cells, is the spark which sets off the anaphylactic explosion, what happens next, what is the explosion? The theory of H-substance attempts to explain this second step of the reaction. It would still be possible to consider this theory, even though the explanation of the first step (antigen-antibody reaction) should later be discarded.

The writer's theory has nothing to do with the first or second step and is not presented as a substitute. It might be termed an explanation of the

third phase, although as with the other two there is no dependence upon the theories of the anaphylactic reaction. It deals with an entirely different problem of the study. My interest is rather in rationalizing the character of the clinical response and correlating it with physiologic functions. One might term it a physiologic theory. It is not submitted as the final truth but as a working hypothesis which will facilitate an understanding of the many-sided aspects of the allergic response. Victor C. Vaughan wrote in 1893, "the value of a theory does not wholly depend upon its truth, but is rather to be measured by the fruitfulness of the lines of investigation that it opens. Indeed, a theory may be wholly erroneous and yet it may lead to most important discoveries."

Basic concepts.—The present hypothesis is based upon the following series of tenets:

There is no fundamental difference between the allergic and the so-called nonallergic individual. The response of the allergic person differs from the nonallergic in degree or distribution, not in kind. It is primarily a protective reaction in which the normal physiology has been disturbed. It is a purposeful reaction, purposelessly executed, a perversion of the function of protecting the body against deleterious environmental influences. It represents a response to an environmental maladjustment. No matter what the location of the shock tissue, it is usually a reversible reaction, representing disturbed physiology rather than an organic pathologic change. Unless the response is too long continued, there is a complete return to normal after termination of the reaction.

The development of symptoms depends in part upon inheritance, in part upon the nature of the allergen, in part upon the degree or duration of exposure.

All persons possess the potentiality of becoming allergic, the susceptibility varying only in degree. It seems probable that in any population the degree of susceptibility to the development of allergy varies from 100 per cent to zero per cent. If we accept the gene theory of allergic heredity it would be more proper to state that about half the population is potentially allergic. It is interesting that these are actually the figures derived from the more recent population surveys.

If 50 per cent or more of the population is allergic in some degree, the question should no longer be "why are some allergic?" but rather, "why are not all persons allergic?" As we have seen, there are graduations from the highly allergic, those with major allergy, through the mildly allergic to those who apparently have experienced no manifestations. One wonders whether there are two groups, or whether there is a gradual merging from one into the other, with the apparently nonallergic capable of becoming allergic under certain circumstances.

In my first survey of one hundred presumptive nonallergies I found the family incidence of allergy the same in both the minor allergic and the non-allergic. Undoubtedly there is a higher family incidence in the frankly allergic. I think there can be no doubt that inheritance increases the predisposition, but this does not necessarily indicate that the capability of becoming allergic does not exist in every individual.

The remainder of this discussion is based on the assumption that 100 per cent are potentially allergic. If future investigations prove that only those carrying allergic genes may become sensitized, the same reasoning will apply to this latter moiety as a group.

Evidence for 100 per cent susceptibility. Spain and his collaborators find that under equal conditions of exposure the percentage of adult human beings susceptible to poison ivy or poison oak varies as the logarithm of the concentration of the irritant applied. This is similar to the response to drugs and other physiologic stimuli in general. We may simplify these conclusions somewhat as follows: A given percentage of persons may be sensitized by patch test with 1:1,000 dilution of ivy extract. If those who failed to become sensitized are now treated with 1:100 dilution, the same percentage can be made to react. If those who fail to react to the 1:100 are tested with 1:10 concentration, the same percentage will react.

This could be interpreted as indicating that, provided the concentration could be made high enough, all would react to *Rhus* "poison." All could be made susceptible, but with varying degrees of "resistance" thereto. There is evidence that this is true of other forms of contact dermatitis.

Krameria or rattany is the dried root of *Krameria triandra* or *K. argentea*, a shrub of Peru and other parts of South America, named after Kramer, an Austrian botanist and physician, who recommended its use as a tonic and astringent in chronic diarrhea and, locally, in leukorrhea and uterine hemorrhage. It is in a separate botanical family, not closely related to other plants. Its use medicinally both internally and applied to the mucous membranes would indicate its general harmlessness as compared with poison ivy. However, Grolnick (1938) found persons positive by patch test and succeeded in intentionally sensitizing 86 per cent of normal subjects by repeated application of the patch test. It is of interest that as subjects developed positive patch tests some experienced flare-ups at the site of previously negative tests. Experimental sensitization to krameria persisted for at least seven months. Natural sensitization has been known to persist at least four years.

Stewart and Cormia produced nickel dermatitis in guinea pigs, constantly, following cutaneous application. They found the lesions similar to those described in man as nickel dermatitis. The intensity of the reaction was in direct proportion to the concentration of the solution used.

From this we could conclude that, given sufficient concentration and enough exposure, nickel dermatitis can be produced in 100 per cent of instances. This corresponds with the early observation of Walthard (1926) that from 41 to 100 per cent of workers in the Swiss nickel industry developed nickel dermatitis. There was an incubation period in these cases of from fourteen to twenty-one days. This suggests true sensitization.

Schittenhelm and Stockinger state that all workers constantly exposed to nickel salts eventually develop eczema. Apparently the degree and concentration of exposure play a great part. Jadassohn remarks that nickel eczema is common in large factories and only occasionally observed in small nickel shops.

These findings correspond to those noted by Spain et al. in ivy sensitization. Bloch has made observations on primula sensitization bearing out the same point. Normal nonallergic persons were rarely found reactive to primula, but when the concentration of the antigen was increased, he overcame this constitutional resistance, producing primula sensitization in nonallergies.

These observations tend to confirm the premise that in dermatitis, even nonorganic dermatitis such as to nickel; in contact dermatitis of the *Rhus* type; and possibly also in atopy, it is possible to sensitize 100 per cent, de-

pending upon the degree and length of exposure. Some become sensitized easily, while others become allergic only in spite of great resistance. There are all graduations between the two extremes.

In making this statement I do not imply that there are not other factors which determine the substance to which one will become allergic, given comparable degrees of exposure. While the experimental findings deal with non-protein sensitization, the cumulative evidence strongly suggests a similar situation with regard to protein sensitization.

If all persons are susceptible to the development of allergy under certain circumstances, and there is no clear cut differentiation between the allergic and the nonallergic, then it is easier to visualize the possibility of the allergic response partaking of the nature of an altered physiologic reaction.

In 1932 the author wrote, "Allergy is not a pathologic state. It is a pathologic exaggeration of a normal physiologic response." In 1934, "The probability is that the development of sensitization to foreign substances is almost a normal physiologic function. If all of us were to live long enough, 100 per cent of the population would develop at least minor allergy."

Rackemann (1930) wrote: "It seems proper to assume that hypersensitiveness is acquired in most cases and probably in all. What we call allergy may well be nothing more than anaphylaxis in man. . . . The production of antibodies in general is a normal function. Allergy is a reaction of a particular kind which is characterized by the easy formation of cellular antibodies in great abundance. . . . When the individual has several different allergic symptoms at one time; when his family history shows allergy in his antecedents, in his children or perhaps in both; when his symptoms are severe or when his skin tests are large, that individual may be assumed to have an easy tendency to develop hypersensitiveness. He is allergic only in this sense." Three years later, writing to the same end, Rackemann found no fundamental difference in the immunologic response, the development of typhoid agglutinins and other agglutinins, in allergies and in nonallergies.

I was under the impression that Rackemann and myself were the first to express the belief that there is no fundamental difference between the allergic and the nonallergic. I find that we were antedated by many years. Doerr who, working with Pirquet, was a pioneer in the study of anaphylaxis stated his belief in 1922 that the capacity to become sensitized is present in all human beings, differing only in degree.

The nature of the allergen plays a part. It has been claimed that there is a fundamental difference between experimental anaphylaxis and human allergy in that human beings can be sensitized to allergens, only with greatest difficulty or not at all; that when sensitization does occur it appears to be entirely spontaneous and probably associated with hereditary predisposition.

It is quite true that Brunner found that he could not easily sensitize individuals to pollen extract or orris root even after repeated injections. On the other hand, he sensitized to ascaris extract with no difficulty.

Jones and Mote found no difficulty in sensitizing humans to rabbit serum. Simon and Rackemann experienced similar success with guinea pig serum, whether administered through the skin or applied to the nasal mucosa. As a matter of fact, the ease with which human beings may be sensitized to foreign serum has been in evidence for many years. The majority of persons who receive therapeutic horse serum develop serum sickness, evidence of sensitization. Hooker has shown that toxins given simultaneously increase the tend-

ency. Twenty-seven per cent of cases receiving toxin-antitoxin subsequently developed positive skin reactions to horse serum. Gordon and Creswell found that 74 per cent of individuals receiving serum who had previously received toxin-antitoxin, gave serum reactions. Forty-three per cent of those who had previously received therapeutic serum (not toxin-antitoxin) reacted after a subsequent serum injection. Tuft found that 28 per cent of children receiving diphtheria toxin-antitoxin became allergic to horse serum.

These observations support my contention that the average person or animal may be sensitized more easily to a foreign protein or substance with which he establishes only occasional contact than to one in which the contact is relatively more constant.

It is difficult to sensitize man to foods which he eats frequently, to feathers, orris root, pollens, house dust—those things to which he is relatively frequently or constantly exposed. Only the 10 per cent who are most highly susceptible to the development of the allergic response become sensitized to common allergens. Those less highly susceptible are more likely to react to antigens which are much more foreign to their economy. This forms the basis of differentiation between the major allergic and the minor allergic.

It is interesting to conjecture that, had the early experiments leading to the discoveries in anaphylaxis been made with substances to which the animals were constantly exposed, the results would have been far different. If guinea pigs eating celery had been injected with celery protein there probably would have been as much difficulty in sensitizing them as occurs when human beings are injected with orris root or pollen extracts. Indeed, it has already been shown that it is as difficult to sensitize animals to pollens as it is to sensitize human beings. If dogs eating beef had been injected with beef extract rather than the extract of sea anemone with which they had never experienced former contact the results might have been different.

Factors influencing sensitization.—Given two potential allergens, to which the individual is exposed in similar frequencies and to the same extent, we cannot state why sensitization occurs to one and not to the other. However, three factors may be recognized.

The first is that of temporary predisposition. Abnormal permeability of the intestinal mucosa associated with gastrointestinal upsets has long been suspected as a predisposing factor in food allergy. The possibility of endocrine influence is suggested by the observations of Bray who finds that boys before adolescence have a higher incidence of allergy than girls, while the reverse is true after adolescence. The menopause also appears to influence allergy in some cases. Fatigue and intercurrent illness may play a part in predisposing toward sensitization. The evidence is chiefly clinical rather than experimental, and at best merely suggestive.

The second factor is that of the nature of the allergen, especially its degree of foreignness. There is also evidence, as seen particularly in the new synthetic chemicals used in industry and in therapy, that a completely new substance to which there has never been previous exposure, is especially likely to cause sensitization. There is evidence such as that reported by Wells in his observations on the sensitization of newborn guinea pigs to oats, and the clinical experiments of Cooke and of Brunner, that it is very difficult to sensitize man or animal to a substance with which his tissues are in frequent or daily contact. If sensitization does occur, daily contact usually results in a response which is similar to desensitization, and symptoms do not ensue.

The third factor is heredity. There is evidence that in a certain group, about 10 per cent of the population, there is the same tendency toward developing sensitization to occasional or new contact substances, and in addition, an inability to desensitize or immunize itself against frequent or chronic contact substances. Possibly the minor allergic also becomes sensitized (with or without positive skin reaction, which is but a manifestation of the state), to chronic contact substances but he does not manifest symptoms because he succeeds in desensitizing himself through daily dosage. But the 10 per cent, the major allergies, have such strong inheritance that even following daily ingestion they cannot desensitize themselves. The intensity of the allergic inheritance appears to play a part in determining this 10 per cent.

Need for a common denominator. An adequate theory of the altered physiology of the allergic response must recognize a denominator common to three groups: experimental anaphylaxis, major allergy, and minor allergy. It must be a denominator that can also be applied in the apparently normal individual. The theory must recognize a mechanism common to all groups. It must include much more than protein sensitization. It is true that the earliest experiments dealt with protein anaphylaxis and they were the most spectacular of the experimental phenomena. They therefore received chief attention. Also, the earliest clinical observations dealt with protein sensitization, such as that to horse serum. And they were spectacular. But, by now, nearly all will agree that clinical allergy involves much more than protein sensitization. Since the earliest work dealt with proteins, and since the early theories were expressed entirely in terms of protein poisoning, it has been difficult for many to overcome the mental hazard involved in the acceptance of a conception of nonprotein allergy. However, by now we have been forced to a realization of the latter as a fact.

The Denominator of Protection or Immunity

A dominant requirement of all life is that it maintain adequate adjustment to its environment.—Primordial life, whether purely chemical, or particulate as exemplified by the amoeba or possibly the phage, depended upon a narrow margin of variation in chemical and physical environmental factors, for its continued existence.

The simple cell aggregates worked out communal methods of protection against deleterious environmental influences. The simplest and undoubtedly one of the earliest was in the protective covering of specially differentiated cells.

In man we find an intricate but withal correlated mechanism of protection against extrinsic factors. This protective system includes the skin; mucous membranes; ciliated epithelium; hairs on the body, in the nostrils, in the ears; the turbinates, uvula and epiglottis; the digestive juices; leucocytes; opsonins and antibodies. Among the more obviously protective reflexes we might mention blinking, the pupillary reaction to light, sneezing, coughing, the gag reflex, vomiting, diarrhea, smooth muscle spasm and the coordinated protective reflexes of voluntary muscles.

Deleterious influences against which the body must protect itself include physical factors such as trauma, extreme changes of temperature, intense light, electricity, ultraviolet, x ray, radium, short wave radio, chemical factors such as acid, alkali, drugs, arsenic, paraphenylenediamine, and biologic factors such as infectious agents, toxins and foreign proteins.

A certain degree of acclimatization is possible by which increased tolerance for deleterious extrinsic factors may be established. While there is some degree of natural acclimatization to atmospheric factors, to poisons, repeated low-grade injury (callouses), and other extrinsic factors, nevertheless this environmental adjustment has rather narrow limits. The morphine addict acquires tremendous tolerance for the drug, but he may still be poisoned with morphine. Our continued existence on this planet depends upon the continuation of an optimal temperature range which is not great. It seems quite probable that many of the species of plants and animals which have ceased to exist have done so because they were unable to acclimate themselves to deleterious environmental influences.

One of the simplest examples of normal increased tolerance is that of adjustment to changes of temperature. The first cool spell in the winter seems colder than a much more pronounced temperature drop later in the season, when one has become adjusted. The first hot days of summer are more enervating than those of midsummer. A person from the temperate zone who moves to the tropics finds that he cannot accomplish as much productive work as formerly until after he has been a resident in the tropics for some months and has become acclimated. This question of acclimatization is, as has been brought out by Duke, an important one in the production of physical allergy or hypersensitiveness to heat or cold.

The simplest heat allergic according to Duke is the one who has allergic symptoms only on extremely hot days. Slightly different is the person who has symptoms earlier in the summer but not in midsummer because by then he has become adjusted. Still different and more difficult to recognize is the patient who tolerates midsummer temperature but not a sudden increase, even though the increase be to a temperature which is not as high as that of midsummer. This is the person who experiences symptoms after leaving an air-conditioned, cooled cinema. The reverse applies to the cold allergic. Where the reaction is manifested more to changes of temperature than to the actual degree of temperature, we find curious situations. Thus the heat allergic may have symptoms only in midwinter when going into a heated house. He cannot tolerate a change from 20 above zero to 70 even though during the summer he had no symptoms at 80. In the summer he had become acclimated. In the winter the change was too sudden for acclimatization. In the same way the cold allergic, according to Duke, may have symptoms only in the summer time. He adjusts himself to winter temperatures but when in the summer he enters an air-conditioned building the sudden drop overthrows his balance.

Complex organisms such as man have built up a complicated system of protective agencies. The allergic response is primarily a protective reaction. —When a noxious substance enters the nose its removal is accomplished by sneezing and the secretion of mucus. The cough, smooth muscle spasm, and increased bronchial secretion of asthma may be looked upon as an attempt to remove a supposed foreign body. Asthma may develop for the first time in connection with a tumor growth in the lung. This is often true asthma and may be relieved by adrenalin or ephedrin. It represents a physiologic reaction, an attempt to remove a foreign body from the lungs. Prompt vomiting which sometimes follows the ingestion of an allergenic food is again a protective response, as is the hyperperistalsis and diarrhea associated with mucous colitis which often follows the ingestion of an allergenic food which

the stomach has not repelled. The serous exudation of a contact dermatitis represents an effort to wash away the noxious substance. Lichenification in chronic dermatitis indicates an effort to establish a protective thickening of the skin at the point of contact. Urticaria and angioneurotic edema which involve internal structures probably to nearly as great an extent as they do the visible integument manifest an effort to dilute the allergenic substance in the body fluids, thus protecting the living cells.

All allergic manifestations are correlated. They are purposeful reactions. They are pathologic exaggerations or perversions of a normal physiologic function, that of protecting the body against deleterious environmental factors.—There is abundant indirect evidence indicating a functional connection, either through the nervous system or endocrine system or both, between the various protective tissues or, better, immunity organs, such as the skin and the mucous membranes. Phillips, for example, believes that pollen hypersensitization can be accomplished more effectively with intracutaneous therapy than with subcutaneous. The fact that the skin reacts positively to a substance such as pollen which causes symptoms on the mucous membrane but not on the skin is further evidence. It seems reasonable to assume some controlling mechanism which integrates the immunity response or protective response of the skin, mucous membranes, glands, smooth muscle, leucocytes and antibodies.

An example might be found in the person who has attacks of diarrhea following therapeutic pollen injections. But here the intestinal reaction does not accomplish the desired purpose. The reactive mechanism is at work but not with effective accomplishment. This brings us to the next point.

The clinical allergic response sometimes manifests itself as a purposeful reaction, purposelessly executed.—The person allergic to house dust who has asthma from inhaling this allergen is experiencing a purposeful allergic response. It is true that the dust cannot be completely removed in this way and the symptoms therefore continue but the purpose of the symptoms is obvious. The baker with asthma from sensitization to inhaled wheat is another example. But when a wheat allergic develops asthma following the ingestion and enteral absorption of bread, the respiratory reaction can scarcely be termed efficacious. In this instance the protective mechanism is in action but is applied through the wrong agency. The reaction is not coordinated.

When the noxious agent acts from within, the same protective mechanism is set in motion. However, in the absence of an external localizing stimulus, the reaction may manifest itself in any or all of the protective tissues or fluids.—The economy of the human body is so arranged that certain tissues serve certain functions. It is supererogatory to detail the various functions, but I would emphasize that when that of protection has been assigned to certain portions of the body the other body cells lose this ability in great measure. Their functions are intrinsic and in a measure much more elementary. For some reason as yet not clearly understood, if the internal tissues or cells come into contact with a foreign protein a certain reaction occurs which, after a preliminary incubation period, makes that protein highly poisonous. The prevailing theories of anaphylaxis have attempted to explain why a foreign protein parenterally introduced, as through a hypodermic needle, becomes poisonous. The present discussion offers nothing new in this regard. Since the Ehrlich hypothesis of antibody formation is the one most generally ad-

cepted at the present time, and possibly the most easily comprehended, we can accept it for this discussion. Suffice it to say that a foreign protein, on second entry into the body, becomes highly poisonous. This has also been shown to be true for some nonprotein substances.

As long as there is a clearly defined external point of contact, the reaction usually takes place in that neighborhood. This is exemplified in the dust asthmatic mentioned above. To mention a rather crude example: if, in a large city with several fire departments, a fire breaks out in a certain locality, telephone communication speedily sends the equipment from one of the engine houses to combat the conflagration. But, assume a large fire in the center of the city. An automatic system sends a general alarm to all departments but the automatic system is not working perfectly and no definite information is given as to the location of the fire. The engines will dash hither and yon to the several more probable places. This is the situation when the reaction occurs within the body rather than at localizing areas in contact with the environment. When the reaction takes place within the body it may therefore manifest itself by asthma, urticaria, colitis, migraine (localized urticaria or angioneurotic edema), generalized edema (acute anaphylactic shock), or by a combination of two or more of these symptoms.

The reaction is protective but the mechanism does not know which area to protect. Certain areas appear to be more reactive than others.

The tropic importance of a contact factor is well exemplified in the work of Auer, of Valy Menkin and of Seegal, who have shown in anaphylactic shock that if a given area is first irritated chemically or by local infection, antigens accumulate in greater concentration in this area and the local reaction is decidedly more pronounced.

This possibly explains some of the allergic reactions that cannot be attributed to the action of the protective mechanism. It is a matter of common experience that patients with true bile tract infections often find that certain specific foods precipitate typical gallbladder attacks. In this case the allergy is an exciting factor, probably attributable to concentration of antigens or reagins at the site of local infection. The same may be true in cases of peptic ulcer.

One might argue that an inhaled substance should always produce respiratory allergy or a substance ingested should always produce gastrointestinal allergy. It has been demonstrated, by the work of Sulzberger and myself, that foreign allergens may enter the circulation through the lungs or respiratory mucosa, causing no reaction therein but producing remote lesions in the skin. Certain of the protective tissues may be more reactive than others. An allergenic food may produce gastrointestinal symptoms or after absorption it may be responsible for asthma, migraine, or so-called neurodermatitis. The same explanation holds.

I realize that Walzer and his associates have demonstrated that foods, when eaten, are absorbed into the blood in a condition still sufficiently like their native state that they can be demonstrated as having reached the skin by the Prausnitz-Küstner technic. But they are not still native proteins, since this phenomenon is quite different from that which follows the parenteral introduction of foreign protein with consequent sensitization. The enteral introduction of protein in the form of food may be followed by ab-

sorption of a substance which is still identifiable as similar, but it has nevertheless already been changed to such an extent that it does not usually produce sensitization.

Certain organs or tissues may be locally sensitized, or more highly reactive than others.—This is an acceptance of Coca's theory of shock organs or shock tissues. If a child's first manifestation of food allergy is asthma the respiratory protective mechanism has become either locally sensitized or unusually reactive. We cannot distinguish which of these two possibilities is correct. If a person has had respiratory allergy for years, reacting with asthma, and later becomes sensitized to a food which likewise causes asthma, we might conclude that this indicates hyperirritability of the respiratory mechanism. But when a specific food causes migraine constantly to the exclusion of urticaria or angioneurotic edema, we must consider a shock tissue, locally sensitized.

We must therefore add the possibility of a local predisposition, to the general picture as described above.

The vagus autonomic system may play an integrating part in the constitutional allergic response.—Vagotonia or vagosympathetic dystonia has for years hung in the background of the allergic picture. I would emphasize that the entire system of cranial nerves is intimately connected with the mechanism of protection against deleterious environmental influences. Pupillary contraction, ocular movements, the senses of taste and smell and of hearing, the sense of equilibrium, swallowing or its absence, the muscular activities of the larynx, vomiting, and the respiratory activities controlled by the vagus, all deal more or less intimately with self-protection. When we recall that the autonomic system includes innervation of the descending colon and the rectum as well, but does not include the small intestines, we see further reason for including the autonomic system in the protective mechanism. The theory of vagotonia as an important factor in allergy is therefore very easily fitted into the mosaic of the hypothesis here presented.

Mental or emotional factors may precipitate the allergic response.—This is seen especially in urticaria but occurs also in asthma, migraine, and less frequently in other allergic diseases. There have been many reports of so-called neurogenic urticaria in which the victim, unable to solve his or her domestic problem, disagreements within the family and the like, reacts with urticaria. This is again an expression of environmental maladjustment. Protein need play no part here. The reactive mechanism, possibly activated through the autonomic nervous system or the endocrine system or both, receives its stimulus from the higher nerve centers, but the site and basis of the reaction are explained in the same manner as in frank allergy.

The endocrine system probably plays some part in the protective mechanism.—The action of suprarenal cortex in preventing anaphylactic shock and of epinephrine in lessening its severity when it has occurred should be mentioned. It should also be recalled that Cannon has elaborated a theory concerning the function of the adrenal secretion in which he gives it a most prominent place in the protection of the individual against deleterious environmental influences. Epinephrine is a "fight or run" hormone. It speeds the heart, raises blood pressure, relaxes bronchial musculature thereby facilitating respiration, diminishes the blood supply to the skin while increasing that to the internal organs thereby giving additional nutrition to the musculature,

discharges glycogen into the circulation, providing an increased blood sugar content for utilization if necessary. Whether the environmental influence calls for combat or for flight the physiologic response to increased epinephrine secretion has provided optimal conditions.

The objection might be raised that epinephrine lessens all of the so-called protective activities which we have described. But it should be borne in mind that the allergic response is a disorganized or disoriented one. We might speak of it as out of proportion to the intensity of the stimulus. It becomes obvious that the adrenal secretion controls the intensity, character and direction of the response. Physiologists have studied the glycogenolytic activity of epinephrine, its action in relaxing smooth muscle spasm, in raising blood pressure and increasing the pulse rate and the like, but there is much that we do not know regarding the effect of this secretion on the tissue cells in general. Epinephrine serves as a balance wheel or a governing factor, controlling the intensity and direction of the allergic reaction. It coordinates it and tends to keep it within normal limits.

The allergic reaction represents a response to an environmental maladjustment. Richet, visualizing a purely experimental phenomenon, and attempting to explain it in terms of immunology, coined the term *anaphylaxis*, indicating the *absence of protection* as contrasted with prophylaxis or *favoring protection*, as observed in the development of immunity. Victor C. Vaughan and Wheeler (1907) were the first to state their belief that the fundamental processes at work in immunity and in anaphylaxis were identical. This concept has been generally accepted.

It is at once obvious that in the theory herein presented, the reactive bodies, which are in essence the protective mechanism of the human body, are the same in allergy as in immunity. In the processes of immunity they react with maximum efficiency, thereby protecting the body as a whole. In clinical allergy they do not fail to react as would be indicated by the term anaphylaxis, but they react abnormally. The reaction is, as I have said, disoriented, disorganized. A more appropriate term would be *dysphylaxis* (difficult protection) or *dysphyl-ergy* (labored reaction of protection). The reaction is of normal type, but apparently uncontrolled.

So-called nonspecific therapy or shock therapy, when efficacious, exerts its beneficial effect by stimulating the reactive mechanism to more effective response.—It is a matter of common experience that an allergic individual often loses his allergic manifestation following an acute illness such as pneumonia, typhoid fever, acute appendicitis, any surgical operation or, indeed, simple anesthesia. The same improvement sometimes follows foreign protein therapy such as intravenous typhoid or colon bacillus vaccine, peptone injections, or even the subcutaneous injection of so-called specific or nonspecific vaccine.

It is probable that all of these stimulate the immunity mechanism, the same mechanism which is responsible for the allergic response, in such a way as to make it more effectively responsive, more efficient, at least for a time. Eventually, however, it again loses its acquired effectiveness and allergic symptoms return.

An integrated reaction. The theory explains the allergic response as an integrated reaction complex, fundamentally protective in nature, but defective in execution since it lacks coordination and a directing influence. It

is, in essence, a manifestation of environmental maladjustment. This is in harmony with the idea recently expressed by Frederick P. Gay, "It is our thesis that the ultimate explanation and prevention of a disease depends on ascertaining its external cause. * * * Not only diagnosis but cure and prevention depend on knowledge of the originating impulse. This impulse, animate or inanimate, is the essential element to discover, and when discovered has invariably been found to be external. * * * We have already expressed our prejudice in favor of the eventual explanation of all disease on a basis of external causation. * * * The cause of disease remains predominantly external."²

The theory materially simplifies our understanding of allergic therapy. The simplest way to circumvent deleterious reaction to a harmful environment is by avoiding this environment. This is obviously the principle of avoidance in allergic therapy. But where the noxious influence cannot be avoided, acclimatization may be attempted, by exposure of the tissues to constant or repeated contacts. This is the basis of hyposensitization or desensitization and accomplishes results in the same manner that acclimatization to deleterious temperature changes produces increased tolerance.

The minor allergic individual may possibly become sensitized to wheat, egg, and milk as easily and frequently as the major allergic, but if he does so, he fails to manifest symptoms therefrom because he readily desensitizes himself by chronic exposure or acclimatization. The person with an unusually pronounced tendency, the major allergic, cannot acclimate himself even with frequent or constant exposure and as a consequence develops symptoms.

If susceptibility to the development of allergy varies from zero per cent to 100 per cent one would expect occasionally to find persons who are allergic to practically everything. Such types, although fortunately uncommon, undoubtedly do exist. I have had occasion to treat a man who was in the produce business, and therefore came into contact with many unusual foods as well as all of the common ones. He was found allergic to 42 different foods, and when tested by the Prausnitz-Küstner technic with the biologic food groups gave positive reactions to 16 of the 30 test extracts. Rinkel has observed certain intractable asthmatics who respond to practically every food with which they are tested. There might be some question as to whether this indicates that they are actually allergic to each of these foods, but there is no gainsaying that, whether allergic or not, they respond to ingestion of all the foods in an allergic manner. Although the reaction may not be specific it is an allergic type of response.

The theory is presented in an effort to clarify our understanding of the manner and meaning of the allergic response and in the hope that, this being better understood, there may be consequent eventual advances in the therapy of the allergic diseases. If the hypothesis contains an element of truth, it should promote investigation in a field which has received too little attention up to the present. Until now chief effort has been given to neutralization or counteraction of a specific response to recognized specific allergens. It seems possible that efforts to develop a nonspecific or physiologic means of controlling the perverted, disoriented reaction of protection so that it may become a normal oriented reaction, might actually lead to the discovery of a remedy which will adequately control the response irrespective of the activating cause.

²Gay, Frederick P.: *Agents of Disease and Host Resistance*, Charles C. Thomas, Springfield, Ill., 1935.

The two lines of approach which from the theory would appear to offer possibilities, deal with the endocrine system, particularly the adrenals, and the autonomic nervous system. Studies in these two fields have until the present been disappointing, but the possibility always remains that, as was true in the case of Banting and Best's discovery of insulin, a somewhat different method of approach may be more successful. There also remains the possibility of the recognition of a new mechanism not identified with either of these two systems.

Summary

The body protects itself against deleterious extraneous influences by means of two processes (a) physiological, or physical, (b) chemical.

Physiological. The skin and mucous membrane form protective barriers. Long hair at the nasal orifices, ciliated nasal epithelium, the large surface area of the turbinate mucosa, the sneezing reflex and increased secretion of mucus are all physiologic protective mechanisms within the nose.

Similar protective mechanisms in the eye include the eyebrow, the eye lashes, pupillary reaction to light and the blinking reflex. In the lower respiratory tract, the epiglottis, the larynx with the vocal cords, the cough reflex, ciliated epithelium, smooth muscle and increased secretion are protective mechanisms. In the gastrointestinal tract we find the gag reflex, nausea and vomiting, sphincter spasm, digestive enzymes, hyperperistalsis, increased mucous secretion. Even in the genitourinary tract we see a protective mechanism in contraction of the smooth muscle of the uterus when a foreign body is present, peristalsis in the ureters in the presence of stone.

It is worthy of note that allergic shock organs, except as will be noted below, are in tissues whose physiologic function it is to protect the body against deleterious extraneous influences. Furthermore, the allergic reaction in these tissues is dynamically the same as that which is called into play in a simple protective response.

Chemical.—In spite of the protection afforded by these gateway mechanisms, deleterious extraneous influences in the form of small particulate matter such as bacteria and complex chemical molecules do sometimes penetrate into the body economy. Even then protective mechanisms are available, but from the nature of the resulting disturbances they are primarily chemical rather than physical. Antibodies, leukocytes and local vascular reactions are the outstanding internal protective forces. These again participate in the allergic reaction. Add to this the transudation of serum as a result of increased capillary permeability, a reaction which occurs in the immunity response to infection, but much more so in the allergic response, and which serves as a buffer to protect the individual tissue cells.

Mechanism. The mechanism of the allergic response is the mechanism of protection and is basically the mechanism of immunity which is a part of protection.

The skin and mucous membranes, the central nervous system and the peripheral nerves extending down to the smooth muscles which they control, are embryologically ectodermal in origin, all derived from a cellular anlage one of whose chief functions is that of protection. Although no physiologic interrelationship has been proved between the protective tissues represented by the shock organs of allergy, the functional interre-

lationship is obvious, and it is reasonable to assume that some relationship does exist. The nervous system may play a part. We have seen in the observations of Thomas Lewis that there is a reflex nervous reaction. The primary wheal is due to local stimulation while the surrounding flare is initiated by true nerve impulses. However, a direct intercommunication between the various shock tissues through the nervous system is not essential in view of what we know today concerning the activity of hormones. The H-substance of Thomas Lewis might possibly be considered as the allergic hormone, a substance which, originating in one organ or tissue, is transported through the blood to other tissues which it stimulates to activity.

Significance.—Wherever within the body the allergic response occurs, that is, whatever the location of the shock tissue, the reaction is a purposeful one, a reaction of protection. However, in allergy it is ineffectively executed. It does not accomplish the desired purpose of removing a noxious agent. Sometimes this is because it cannot be removed by this method. Examples are seen in house dust or feather dust in the bronchial tree or a foreign body or malignancy in a bronchus. Nonetheless the physiology of the response is that of protection even though, instead, it results in symptoms of severe illness.

The intensity of the reaction appears to be entirely out of proportion to the strength of the stimulus. The inhalation of dust to which an allergic is sensitized elicits a response more violent and less effective than the inhalation of the same dust by a nonallergic. To a degree the response appears to incline toward maximal, rather than being proportionate to the intensity of the stimulus. The theory offers no explanation for this.

There is ample evidence of local sensitization within the body. The person who always experiences colitis following the eating of sweet potatoes, and who always has migraine after Irish potatoes and who after the ingestion of cherries experiences neither colitis nor migraine but consistently has attacks of urticaria, is an outspoken example of local sensitization in one or another of the shock tissues.

Whatever makes a person allergic (and this we do not know as yet) makes one or another, or all shock tissues abnormally responsive, so responsive that they over-react. If we continue to accept the antigen-antibody hypothesis and the H-substance theory, then we can say that local contact with the allergen results in a discharge of H-substance which produces a local purposeful reaction of protection. If the stimulus is stronger or if the response is stronger, some of the H-substance passes into remote shock tissues which may be stimulated, either through the blood or some nerve mechanism. Thus, a hay fever patient, following an injection of ragweed extract, has a severe local reaction, hay fever, and an attack of abdominal pain with colitis. Possibly, sufficient H-substance was discharged from the local reaction at the site of injection to stimulate the shock organs of the intestinal tract as well as the nasal mucosa.

If the allergenic substance, the noxious agent, first makes its appearance inside the body, as following parenteral administration or enteral or respiratory absorption, the clinical response may manifest itself in any or all of the shock tissues, depending upon whether they are locally sensitized to the allergen or upon how responsive the various shock tissues are to the stimulus of the H-substance. Therefore, following parenteral administration

one may observe skin reactions, bronchial tree reactions, gastrointestinal or vascular response. All may react or the reaction may be so explosive as to be localized in no gateway shock organ but generalized, with the symptoms of anaphylactic shock.

For some as yet incompletely understood reason, a person becomes sensitized to a foreign agent. Antibodies are formed. Following second exposure to this agent, the foreign substance becomes attached to sessile antibodies. This damages the tissue cells, resulting in the release of H-substance. H-substance stimulates one or several shock organs to a protective response. This purposeful response tends to be maximal and ends up by being ineffectual. Its significance is obvious, its execution appears to be purposeless. The resulting phenomena are the symptoms of clinical allergy.

CHAPTER XVI

AN APPROACH TO A PHYSIOLOGIC INTERPRETATION

A comprehensive understanding of the phenomena of allergy will be hastened if we approach the problem not only from the chemical point of view but also from that of physiology. The process of living is one of adjustment and readjustment to one's external and internal environments. Adequate environmental adjustment is termed immunity. I do not use the term in its bacteriologic sense but in its broader significance, including all modes of protection against deleterious influences.

We may look upon extrinsic allergenic excitants such as pollens, foods, contact allergens and physical agents as a part of one's environment to which the normal person adequately adjusts himself, with resulting immunity or freedom from symptoms. Intrinsic excitants such as bacteria may be looked upon in the same way, but for simplification of the present discussion we will limit consideration to the extrinsic, both atopic and nonatopic.

A broad viewpoint.—Let us investigate the possible ramifications of the rather philosophic concept that the allergic reaction represents a failure in adaptation to an environmental influence. We shall see that it takes us far afield in speculation. This is excusable if, by the adoption of a new point of view, it tends to clarify the picture. We are still in search of the common denominator. The subject of allergy has too long been characterized by a large number of poorly correlated phenomena.

For orientation, I shall present several very brief case histories illustrative of my contention that the clinical allergic response can nearly always be shown to be associated with failure of satisfactory adjustment to environmental problems, even though the problem, or shall we say the allergenic excitant, be purely mental. Furthermore, the symptoms are the same as those which follow exposure to atopic excitants.

Psychogenic factors: illustrative cases.—

A young lady in her late teens complained of urticaria. Sensitization studies failed to demonstrate any allergenic excitant. After unsuccessful efforts with trial diets I discovered that she was attempting to break off relations that had become no longer friendly, with a young man. Following instruction she terminated the affair, after which her urticaria was relieved. Three months later she returned with more urticaria. It developed that the young man had refused to consider his affair terminated and had recently created several unpleasant situations. We consulted the judge of the Juvenile and Domestic Relations Court who directed a police officer to notify the young man that persistence in his importunities would speedily result in a court experience. He promptly desisted and in the ensuing five years she has had no recurrence of urticaria.

This young lady had had a problem which she could not solve. The somatic response appeared in protective tissues. The problem having been adjusted, her symptoms were relieved.

A middle-aged man complained of urticaria. He reacted to a house dust extract. Desensitization was given for a period of a month, after which he was relieved. Several months later he had a recurrence. Another course of dust extract was followed by relief. About one year later he had a third and final episode which was again treated, with relief in a few weeks. This was recorded as a case of urticaria associated with inhalant allergy until several months later, when we inadvertently learned the truth. The patient was married to a woman many years his junior. The first of his three allergic episodes occurred when he discovered that his wife had become dangerously interested in another younger man.

Either he adjusted himself to the new situation or became convinced that his suspicions were unfounded. The second attack occurred when she announced that she was leaving him, to procure a divorce and marry the other man. This she did. The final attack was brought on upon receipt of a letter from his former wife asking him to send her the bedroom furniture which had been her property.

Both of the cases so far cited were persons with ample emotional reserve, not in the habit of discussing their problems with others, or of having rages, tantrums or weeping spells which might have called the adrenal glands into activity. This is also true of those which follow.

A young woman of twenty had urticaria, which was always relieved when she left home. She was objectively allergic, reacting to a number of atopens, none of which were shown to cause symptoms. Prolonged discussion developed that a very dear relative was a chronic alcoholic and that she was devoting her life unsuccessfully toward persuading the relative to forswear alcohol. At the same time she felt it her duty to refuse a suitor, with whom she happened to be very much in love. The situation appeared to be quite hopeless.

A stock broker of 48 had severe urticaria during the first turbulent months of the depression. Sensitization studies revealed nothing pertinent. Four years later at a time when there was no emotional problem whatsoever he had recurrence of urticaria during the melon season, proved to be due to melons.

In this case as in all except the first, there was other evidence of allergy, usually atopic in nature, that is, with associated positive scratch or endermal skin reactions. This man's first episode was emotional in origin, and relieved when his business problems were satisfactorily adjusted. His second episode was purely atopic.

A woman who knew that she had been allergic, reacting with urticaria to shrimp and chocolate, but who for several years had eaten them with impunity, had word that her mother had been in an automobile accident. She promptly developed urticaria, hurried to her mother's bedside, to find her injury very mild. In spite of the fact that her emotional problem was thereby adjusted and that her mother left the hospital the following day, urticaria continued. She was found allergic to shrimp, chocolate and strawberry. Their elimination resulted in amelioration but not relief of symptoms. She was then found allergic also to Coca-Cola, which she drank daily. Following the avoidance of this also, urticaria disappeared.

Here was an allergic individual known to be sensitized to certain foods which she was eating, but in a state of balanced equilibrium, and free from symptoms. A psychic upset precipitated recurrence which was not relieved following emotional readjustment, but was kept going by the specific foods. The allergic balance had been upset.

These have all been instances of emotional or psychogenic urticaria. Other allergic symptoms may follow emotional disturbance. A middle-aged, childless, married woman developed hay fever and urticaria whenever she saw her sister-in-law's baby. The unmarried sister who had become pregnant had come to live with the patient and her husband. The child was born in her home. To prevent gossip she and her husband had adopted the baby and became devoted to it. The sister-in-law moved to another city. In December, 1936, the actual mother, who had in the meantime married the father, returned to claim the baby. Many unpleasant episodes ensued, during each of which the patient developed vasomotor rhinitis and urticaria. Finally to prevent a legal battle the patient and her husband relinquished the child. Since then, whenever she goes to see the youngster, or he comes to her home, she has paroxysms of sneezing with urticaria. As long as she stays away from the baby she is free from trouble.

A young medical student with angioneurotic edema and urticaria due to eggs and tomatoes invariably experienced attacks of the former when boning up for examinations. A woman singer who often gave concerts but was always very apprehensive about them, usually had attacks of angioneurotic edema just prior to the concerts. A woman with intrinsic asthma was in an automobile accident with her husband. Since then, when she rides with him and he applies the brakes suddenly or when she thinks he should, she promptly becomes asthmatic.

An asthmatic woman in her early twenties was very much in love with a man slightly older than herself. Unfortunately he did not share the sentiment but was quite unconscious of her problem. She found it necessary to conceal her emotions when they were together. Whenever she was alone with him she promptly developed an acute attack of mucous colitis.

These illustrative cases almost run the gamut of the common allergic manifestations. Duke has mentioned similar cases. I am indebted to my friends for the description of the following unpublished cases.

Tuckwiller's case is that of a stenographer with vasomotor rhinitis due to the common inhalants. When her employer died she developed urticaria and migraine. Eyermann's man developed angioneurotic edema when losing at poker, not when winning. Hansel's patient with migraine was allergic to wheat but tolerated it in moderation. Following an emotional upset while eating the customary amount of wheat, he had recurrence of migrainous attacks which were ultimately relieved by wheat avoidance. A woman on perennial pollen treatment, with dosage held constant, had a severe emotional upset shortly before one of her treatments. This treatment produced a constitutional reaction even though the dose was not increased. For some time thereafter, the dosage had to be reduced. Swineford's case was a student who had vasomotor rhinitis whenever, in the parlance of the campus, he "was making time with a girl." His fraternity brothers found that emotional upsets would give him hay fever. Thereafter, they would poke fun at him at the dinner table to make him sneeze. I have a similar case, a young woman who has an episode of sneezing whenever she must make any decision which she considers very important.

These cases could be multiplied, and I am sure that if we would spend enough time discussing their problems with our chronic allergies, we would find that allergic episodes are often precipitated by purely psychic factors, usually connected with some difficulty in one's emotional adjustment to environmental problems. The fact that the majority are otherwise allergic, suggests the intriguing hypothesis that some common physiologic factor may be found.

Can we call these psychogenic reactions allergic? Or must we dismiss the subject by saying allergic symptoms may be caused at times by allergy and at other times by quite unrelated emotional factors? When we speak of nervous asthma or urticaria must we designate an entirely different category of disease? Or are we justified in using the term psychogenic allergy or emotional allergy?

This could be done only with a new conception of allergy and a new interpretation of the term. As a matter of fact, it is high time that we should develop a newer and broader understanding of the process. I believe that this can be done if we will adopt a physiologic, rather than a chemical, attitude.

Evolution of the allergic picture.—It is curious that in the allergic diseases our approach has almost without exception been a backhanded one, a reversal of the usual procedure of experimental investigation. In diseases such as nephritis, diabetes, tuberculosis, poliomyelitis, the clinical picture and pathology were well understood before attempts were made at experimental reproduction, and study in laboratory animals. The reverse situation holds in allergy. Here, laboratory investigation anteceded clinical recognition. Richet, Rosenau and Anderson, Otto, Vaughan and others had been working for several years on the curious experimental phenomena known as anaphylaxis, before Weichardt, Wolff-Eisner and others suggested that certain clinical diseases might be based upon a similar process. Then, a curious situation developed. Some very excellent investigators were so impressed by points of dissimilarity between clinical allergy and experimental anaphylaxis that they insisted that the two could not be identical. Certainly, there were very many more points of surprising similarity. Experimental anaphylaxis resembles clinical allergy every bit as much as experimental nephritis resembles Bright's disease. The outstanding difference is that in the customary sequence of investigation we found the cart before the horse, in allergy.

Granting a basic identity between anaphylaxis and allergy, we soon meet another hurdle. The early work was done with protein. Even on the clinical side, the startling symptoms such as serum reaction followed contact with allergenic proteins. The term *protein poisoning* was coined. Protein anaphy-

laxis is the most spectacular of the allergic manifestations. Consequently, it was the one most readily recognized in the days when we were just becoming acquainted with the phenomenon.

Soon it was found that drugs, not protein at all, could cause similar reactions. But by now we had become accustomed to think in terms of protein. There was, therefore, great division of opinion as to whether drug idiosyncrasy could be classed as truly allergic. Wolff-Eisner, Obermeyer and Pick, and Landsteiner came to the rescue with the concept and demonstration of haptens. We could still talk in terms of protein allergy.

Unfortunately, however, there were still more hurdles. Along came contact allergy. Here the exposure was on the surface, and it was difficult to visualize a combination of the allergen with the proteins of the body fluids to make a hapten complex. Of course, one could still ring in proteins by speaking of a combination of contact substances such as soaps, dyes, metals, etc., with the protein of the tissue cells in the skin. But this was a far cry from our original concept of protein anaphylaxis.

Next, we were introduced to physical allergy. Here at last it was no longer possible to ring the old familiar bell of protein sensitization. One finds it very difficult to visualize a combination of heat or cold or sunlight with body proteins to make a new protein. I look upon the recognition of physical allergy as a most important step in our backward progress to an understanding of the pathologic physiology. This, not only because it necessitated a break from the older concepts which were based on the more spectacular allergic manifestations but also because it introduced the concept of physiologic acclimatization, a concept which is applicable to all types of allergy, from first to last.

All of this evolutionary development has been backward. It is as though we had studied a microscope slide intensively with oil immersion lens before switching to a low power, where the perspective is broader. It has progressed backward from the startling early laboratory observations to their clinical analogies, and then, spreading, still backwards, to take in a much wider scope of clinical phenomena, but all having this one thing in common—that the reactive mechanism is always the same, the familiar shock organs or shock tissues of Doerr and Coca.

Finally, we have now come to cases in which the same shock tissues were activated by purely emotional excitants. Surely there must be somewhere a common denominator which will integrate all these clinical reactions. Obviously, this denominator cannot be protein or protein sensitization.

Physiologic approach.—We should realize that just as one may study gross and microscopic pathology, so one may examine gross and micro allergy. The chief difference is that we have still been doing it backhandedly, studying the micropathology of allergy, its chemistry, and have paid scant attention to its gross phases. The latter are represented by the altered physiology of the allergic response. It is in an interpretation of this latter that we may carry our understanding one step still farther backward, from side-chains and H-substance, one step nearer to a picture of the whole.

If this is to be done we must alter our terminology from that of immunochemistry to that of physiology. The writer does not presume to add any new concept in physiology nor is he under the impression that the physiologic observations to be presented explain all of allergy. As a matter of fact, if the concept serves no greater purpose than as a connecting link between immunochemistry and the pathology of the physiologic response, its purpose will have been fulfilled.

The autonomic system. Many years ago it was suggested by Pottenger and others that the vagus autonomic system appears to be hyperactive in asthma. From this came the suggestion that asthma and possibly the other allergic diseases are associated with a condition designated as vagotonia. Since then the term has been accepted in a very general way as being often a part of the allergic picture, but there has been little investigative work on this line in allergy. On the other hand, there has been much study of the physiology of the autonomic nervous system. Let us review this more recent work, observing how well it may fit into the jigsaw puzzle of allergic physiology.

In 1909 Eppinger and Hess suggested an antagonistic balance between the sympathetic and the parasympathetic or vagus autonomic systems. Preponderant activity of the parasympathetics resulted in a condition known as vagotonia; of the sympathetics in the reverse state of sympathicotonia. There were many objections to the concept of these investigators, but the idea still holds, in modified form. Our present knowledge is briefly as follows:

Sympathetics.—The sympathetic division of the autonomic system takes its origin from the gray matter of the thoracic and lumbar spinal segments. The parasympathetic division is supplied by the cranial and sacral autonomic nerves. In the sympathetic divisions the ganglia are close to the vertebral column, remote from the final distribution of the nerves. Cannon points out that an important feature of the sympathetic system in addition to the extensive distribution of its fibers, is its arrangement for a *diffuse* discharge of nerve impulses. The system with its remote ganglia, all interconnected, is so arranged that it may act as a whole. This unitary action is the most significant aspect of the sympathetic system. It explains its high efficiency in securing adjustment to one's environment. It provides for the mobilization and ready utilization of energy.

Unitary stimulation of the sympathetics results in increase of the pulse rate; vasoconstriction in quiescent regions, especially the splanchnic area with simultaneous increase in blood flow through the active tissues, especially muscles; dilatation of the bronchi to facilitate the entrance of oxygen and discharge of carbon dioxide; increase in the number of red cells which carry oxygen; increased activity of the sweat glands to provide loss of excessive heat; mobilization of glucose in the blood for energy; and hastening of clotting of blood. It will be seen that sympathetic activity produces the same responses as adrenalin, responses which provide for rapid and adequate adjustment to environmental difficulties. These difficulties have usually been spoken of as those of combat or flight. Adrenalin has been termed the fight-or-run hormone. The energy requirement for either situation is provided for, either by discharge of adrenalin into the blood or by sympathetic stimulation. Thus the stimulus may be neurogenic or hormonal. The evidence at present is that adrenalin is not discharged except in an emergency. It is an **emergency hormone**.

Sympathetic discharge is useful in adjusting to physiologic needs other than those of combat or flight. Totally sympathectomized animals continue to live without difficulty, free from functional deficiencies, so long as they are not subjected to conditions of physiologic stress. They are no longer able to adjust themselves adequately to changes in temperature. It has been shown by Cannon that sympathectomized animals are unable to maintain a constant protective internal environment of the tissue cells. This applies, for example, to the tissue fluid, outside the vascular system, surrounding the tissue cells

Anger and excitement sometimes relieve allergic symptoms, possibly due to increased adrenalin discharge or increased activity of the sympathetics. A patient found that whenever he became excited or angry during an attack of asthma the latter was relieved. It is said that William the Conqueror was asthmatic but that in the heat of battle his symptoms were relieved.

F. P. Gay's conclusion that bacterial infection produces sympathetic stimulation may explain in part occasional relief from allergy, for a period, following acute infection. Sympathetic activity for a time overshadows parasympathetic activity.

Parasympathetics. Turning now to the parasympathetic divisions of the autonomic system, we find a very different anatomical layout. In its distribution and in the number of effects which it evokes this system resembles the sympathetic. A majority of the viscera are innervated by both. But the striking difference is that the ganglia lie either within or close to the organs innervated. They are not remote and closely interconnected but are very near the organs controlled and only remotely interconnected. The restricted distribution of the ganglia facilitates central nervous system effects upon single organs in contrast to the widespread sympathetic influence.

Applying these differences in allergy, we may see a possible physiologic basis for the fact that the clinical allergic reaction usually occurs in certain localized tissues known as shock organs, usually innervated by the parasympathetics, but that no matter where the localization, no matter which shock tissues are affected, adrenalin gives relief. We are dealing with general stimulation of the sympathetic which may be counted upon to overcome local disturbance in the parasympathetic, wherever the disturbance may be. Bard* writes, "The characteristic anatomical organization of the parasympathetic is correlated with absence of unitary action in the system. Should this division go vigorously into action as a whole there would be produced widespread coincident changes bearing no functional relation to one another; the results would be disorderly and purposeless." To me it is stimulating to consider this as a possible mechanism of allergic shock, in which the response is disorderly and purposeless.

The question naturally arises: if there is a hormone, epinephrin, capable of stimulating the sympathetic system to activity, should there not also be a comparable hormone for the parasympathetic system? The existence of such a hormone has recently been demonstrated. Evidence so far indicates that it is acetylcholine or some very closely related substance. Loewi (1921) exerted vagal stimulation on a frog's heart in Ringer's solution, until the organ was slowed or stopped. He then found that the Ringer's solution was capable of exerting a similar effect upon another, nonstimulated heart. Something had been secreted into the Ringer's solution. He spoke of this as "Vagus substance." There has been considerable confirmatory evidence. For example, a perfusate passed through the vessels of the tongue which have been actively dilated from stimulation of the lingual nerve, has a typical vagal effect on intestinal muscle. Locke's solution passed through the vessels of a cat's submaxillary gland during stimulation will inhibit the isolated frog's heart, will increase the activity of isolated intestine, and will promote salivary secretion.

Recent evidence indicates that this parasympathetic hormone is secreted locally by the terminal nerve fibrils of the parasympathetic system and that

*Bard, Philip: *Macleod's Physiology in Modern Medicine*, The C. V. Mosby Co., 1935.

it may affect contiguous cells or tissues but that it does not normally exert an action on remote tissues or organs similarly innervated. This is because it is rapidly destroyed in the blood. The parasympathetic hormone or mediator appears to be a very active but highly labile choline ester, in all probability acetylcholine.

The choline bodies, especially acetylcholine, produce effects similar to those of vagal stimulation. The activities that have been studied more extensively are stimulation of intestinal contraction, lowering of blood pressure, cardiac slowing and increased activity of glands such as the lachrymal, salivary, etc.

Although acetylcholine is rapidly destroyed in the blood it has been shown that physostigmine (eserin) prevents this rapid breakdown. Using a method based upon this fact, Wenner and Buhrmester have shown that the blood of rabbits in anaphylactic shock contains relatively large quantities of acetylcholine. The blood of sensitized rabbits reacting short of shock contained smaller quantities of acetylcholine. That of control rabbits contained none.

We may say that the sympathetics and parasympathetics normally maintain a balance which promotes adequate adjustment to certain environmental exigencies. Too little sympathetic activity or too great parasympathetic activity disturbs this adjustment. The result is hyperactivity or vagotonic manifestation in one or more of the organs or tissues innervated by the parasympathetics. Many of these tissues correspond to the shock organs of Doerr and Coca. The locally secreted mediator or hormone appears to be acetylcholine. This is produced in tremendously increased amounts in anaphylactic shock, where it may be demonstrated in the blood.

One cannot speak of vagotonia alone, since the same results may be produced either by parasympathetic overactivity or by sympathetic underactivity. It seems to me far safer to speak of autonomic imbalance.

To me it is an attractive hypothesis to add to the theories of allergy, that: tissue cells having been injured by a combination of antigen with sessile antibody or by some as yet unknown disturbance in colloidal equilibrium; H-substance is liberated from the damaged cells; this in turn stimulates the parasympathetic system to various grades of activity, depending upon the quantity of substance liberated. The picture of the clinical allergic response then becomes logical and explainable in terms of physiologic processes. H-substance is not identical with acetylcholine. There may be and probably is an intermediate reactive agent. This problem requires investigation.

In none of these theories do we find an explanation why a person becomes allergic to one substance, not to another, why adjustment may fail to only one out of many environmental excitants. This remains an enigma. Possibly further study of the heredity of allergy as suggested by Coca, may eventually solve this problem. To me it seems probable that in discussing predisposing causes we must add the factor of autonomic imbalance to that of hereditary predisposition. This in turn may depend in part on heredity. Here is another problem deserving of investigation.

Emotion and the conditioned reflex. Let us return now to further consideration of the subject first discussed, the emotional factor in allergy. Having presented the hypothesis of a neural integration in the reaction and in view of the well-known influence of the emotions on the autonomic system, especially the sympathetic, we can now see a possible reason for symptoms of psychic origin indicating parasympathetic preponderance.

There are two general types of emotional individuals. Members of the first react with those symptoms which may be attributed to sympathetic activity or adrenal discharge; anger, physical combat, restlessness, even hysterical outbursts. The second type psychologically and physically exerts much more self-restraint. He is less likely to discuss his problems with his friends and his emotional response may be described as internal rather than external. Such a person may be looked upon as more preponderantly of the parasympathetic type.

Need a person with allergic symptoms associated with psychic inhibitions, necessarily be otherwise allergic? One of the aforementioned cases showed no other evidence of allergy, but all of the others had atopic allergy as well. Menninger and Kemp's case of psychogenic urticaria was not otherwise allergic. This is a problem for collaborative investigation with the psychiatrist. At the same time, it is obvious that for best results in all cases it behooves the allergist to give ample attention to his patient's emotional problems. They may be primary or of only secondary importance, but I will venture to say that if time enough is given to their consideration it will be found that the mental factor enters into the majority of cases of "ordinary" allergy.

As an illustration I will mention three clinical experiences which indicate that even conditioned reflexes may play a part in emotional allergy.

A middle-aged woman was allergic to watermelon, reacting with nausea and vomiting. This had occurred so many times that, as she said, she "couldn't stand the sight of a watermelon." When she would go into a dining room where sliced watermelon was on the table, merely the sight of it caused her to react with nausea and vomiting.

Lee* conducted an interesting experiment in the 1937 grass pollen season. The atmospheric pollen count was chalked on a blackboard each day, where his patients could observe the course of the grass curve. In the middle of June he intentionally chalked an erroneous count 500 higher than the counts had been running. There was no actual increase in pollen concentration. Nevertheless, before the end of the day three of the many patients who had seen the chart developed severe exacerbation of symptoms.

The third case which may well be an example of conditioned reflex is the historical one described years ago by Widal. Widal persuaded a woman who was convinced that her asthma was due to roses to smell a rose. She did not know that it was an imitation rose. But she promptly developed asthma. This case has often been mentioned, rather in derision of the tenets of allergy, but to me it appears to be a very good example of the conditioned reflex, in a person with atopic allergy.

Allergy in the insane. Returning to the writer's tenet, that the allergic reaction is usually associated with failure of satisfactory adjustment to some deleterious environmental influence, a failure of immunity, we find further confirmation in the field of psychogenic allergy. There is evidence which suggests that the allergic response occurs in the psychoneuroses but not in the psychoses. The psychoneurotic person is still attempting to adjust himself to his environment. One with true psychosis is no longer interested in his environment, at least to the extent of attempting to make rational adjustment. Once a psychoneurotic becomes psychotic, allergic symptoms disappear.

Gillespie (1936) quotes cases in which manic-depressive psychosis alternated with asthma, the latter ceasing at the onset of either elevation or

*Lee, Howard, Oshkosh, Wis. Personal communication.

depression and reappearing after its subsidence; and cases of dementia precox in which asthma ceased at the onset of severe mental symptoms.

Janet found mucous colitis rare in true psychoses. If the symptoms of mucous colitis are present in an individual who later develops a psychosis, he states that the abdominal symptoms disappear throughout the psychotic period. MacInnis reported that in two insane asylums, each with 3,500 patients, one had no allergic patients while the other had had five cases, asthmatics, in the last five years. Three of the five remained free from asthma during their mental illness with return of symptoms each time their psychoses were cured.

Hawke tells me that among 3,000 persons in the New Jersey State Hospital only eight had clear-cut allergic manifestations. Cable, of the Central Oklahoma State Hospital, in a communication to Bowen states, "We have always noted that seldom do we have allergic diseases arise among our inmates here in the hospital. This has been noticed for years. We frequently have it among our personnel but seldom among our patients. Just at the present time I know of but two cases among the women and two or three among the men and we have a population here of 2,500." These were cases of asthma. This surprisingly low incidence of allergy in the insane is to be contrasted with the 7 to 10 per cent major allergy in the general population. This suggests that an adequately functioning nervous system is in some way necessary even in the commoner forms of allergy.

On the other hand, it should be noted that Walzer* finds hay fever not uncommon among psychotics, and that they accept passive transfer in a normal manner.

Conclusions

The routine treatment of allergy, today, is in essence the treatment of the allergic episodes. It is not the treatment of the basic condition. The generally good results and the absence of a clearer understanding of the basic physiologic processes justify the procedure. For the present we must content ourselves with the control of specific allergic reactions, either by means of avoidance or by acclimatization, the process which is generally termed desensitization.

I believe that the future holds the possibility of control of basic predisposition entirely independently of specific sensitization. Then, we shall speak of hypoallergesis, general lessening of the allergic tendency, as well as specific hyposensitization.

The observations herein recorded are not presented as proofs of the suggested mechanism. They are, however, facts which require explaining, and which form an attractive framework on which to build a plausible approach to a physiologic interpretation of the allergic constitution.

Emphasis on the emotional or psychic factor in the allergic diseases is not new. Psychiatrists stress them particularly, often to the exclusion of the possibility of concomitant allergy. Allergists have probably not stressed the mental factor enough, although the writer is by no means alone in directing attention to the problem. John Freeman, coworker with Noon in the inauguration of modern allergic therapy, wrote (1935):

"There is a fifth and psychological way in which a particular toxic idiopathy may be selected by the body. In this respect I stand between the devil and the deep sea because, whereas the nonpsychologists will tend to pooh-pooh such a fanciful idea, the psychologists

*Hawke, Ed.; Bowen, Ralph; Walzer, Matthew: Personal communications.

will say that I do not go far enough; also they will probably think that we nonpsychologists have no right to dabble with the subject. To the psychologist asthma is an anxiety neurosis, and he may say that the patient, finding insuperable resistance to the conscious expression of his emotions, resorts for the purpose to some psychological function such as breathing, which thus becomes pathological, i.e., asthma. Psychologists would say that the patient would unconsciously select the toxic idiopathy most symbolical of being shut-in or choking spiritually. I will illustrate this with two cases. . . . In neither of these cases was the psychological factor the 'sole cause' as some psychologists would like to claim, but I think that we cannot overlook the possibility of a psychological disturbance thus starting one particular type of toxic idiopathy.'

The inauguration of a study of the psychogenic factor in asthma at Guy's Hospital, London, was given editorial comment in the *Journal of the American Medical Association* (1936). The British investigators found the intelligence of the asthmatic group above average.

Gillespie (1936), continuing the study at Guy's Hospital, wrote:

"It is not my contention that psychological factors in themselves can be a sufficient cause of asthma, but rather that asthma, in the sense of the characteristic attacks, is a peculiar mode of reaction of certain individuals to a variety of stimuli, and that these stimuli may be either of a physical or a psychological order. . . . Asthma can also furnish a striking text of what needs to be emphasized in the education of medical students: that the body and the mind are one; or at least that their interaction is so close that no examination of a patient should neglect some consideration of what is going on in his mind. We shall see how far in certain cases of asthma diagnosis, in the causal and not in the merely symptomatic and nosological sense, and treatment may both be wrong if the possible psychological factors are left out of consideration. . . . Every emotion tends to be propagated like a wave of physiological disturbance through the vagal and sympathetic systems to the viscera. If there is already existing some disturbance of the vagosympathetic, clearly the emotional disturbance will have unusual effects, and asthma may be one of them."

Gillespie states that he has seen asthma occurring as the accumulation of an anxiety, as expressing an emotional conflict, as a protest against an unwelcome situation, as a means of escape, and as a conditioned response. "We find that almost every conceivable type of relationship between psychological factors and asthmatic attacks can be demonstrated by taking a sufficient number of asthmatic patients into consideration."

Clarkson summarizes observations on the nervous factor in 187 patients with ages ranging from 2 to 20 years. He found that the psychological element intruded in varying degree in almost every case but that it was rarely the sole cause. "In 98 per cent of my cases I have not been able to demonstrate a purely psychogenic cause for the onset of asthma in the absence of other factors."

An objection might be raised to the conception of a psychic genesis of asthma or other allergic disease as based upon failure in adaptation to an emotional problem in the fact that such an explanation would rarely be found to hold in allergic children in whom such a problem would rarely exist. Strauss (1935) explains this in finding that the emotional status of asthmatic children is both overanxious and insecure. He finds asthmatic children either to have been very much "wanted" by their parents or very much "unwanted." They are children who are fussed over needlessly and who subconsciously absorb anxiety expressed by their parents concerning their welfare.

The present writer is more impressed with the explanation by Clarkson who likewise finds that parental invasion of the child's psychic life markedly influences his affective state, and that the allergic child is often made aware of disordered emotional currents in its allergic parents, and tends to fashion its own reaction in a "preselected" imagery.

The outstanding feature of his conclusion however is that the allergic factor is the usual one responsible for onset of juvenile asthma. Asthma having been inaugurated as a manifestation of allergy, the psychic factor may then precipitate individual attacks.

“This condition applies only to the early stages of the syndrome. When the condition has continued for sometime diffuse psychical reactions centering around the organ inferiority emphasize the preexisting emotional fears. . . . In asthma frequent autonomic hyperirritability, initiated by allergy, is an ideal furrow for the formation of fear complexes. . . . Once the experience of bronchospasm is sufficiently repeated there can be no doubt that it acquires all the characteristics of a conditioned reflex. . . . On the somatic side the activity of almost every organ under control of the vegetative nervous system can eventually be the trigger of vagosympathetic imbalance. Thus it is that a loaded rectum, a swollen middle turbinate, or a distended stomach may initiate a spasm. Correspondingly, the diffuse ramifications in the psyche centralized around the primary emotional nucleus of fear may at any point lead to an attack. . . . There tends to be a perpetuation of an intense emotional life, maximal when the allergic balance is upset, and the establishment of an habituation reflex, the primary nuclei of which are grouped around fear.”

The factor of suggestion is well illustrated in the following case. An eight-year-old girl with perennial vasomotor rhinitis was being studied allergically. Her mother hovered apprehensively over her. The child sneezed most of the time. After the second day we persuaded the mother to return home so that the study could be continued with less commotion. In the succeeding five days of the examination, the child had no attacks of sneezing whatsoever.

Both Gillespie and Clarkson report relief of attacks by hypnosis and suggestion. The latter describes an asthmatic girl with a very strongly positive skin reaction to egg, a wheal one inch in diameter with flare $3\frac{1}{2}$ inches across who was later tested with the same extract while under hypnosis. The skin reaction under hypnosis was negative. The following day when the patient was not under hypnosis, the skin test was again strongly positive.

To the writer it appears that the time is ripe for the inauguration of collaborative studies by the allergist with the psychiatrist as has been done with the rhinologist.

PART IV

ALLERGIC DIAGNOSIS

At the present time we would probably all agree that the present method of attack: that is, removal of what seem to be significant allergens, as determined by skin hypersensitivity, the history, and possibly by elimination diets, is the best immunologic approach now available, and that there is considerable evidence to show that it is founded upon sound principles; furthermore, that it sometimes works.

It does not, however, solve the problem. It is fairly good, but not good enough; one cannot be satisfied with it; it is not effective enough to make one feel that this is all there is to it, and that he has a really adequate therapy at hand, even when combined with all other possible measures. There is a large gap which must be filled if this disorder is ever to be understood, and I think that those of us who have been especially interested in it, although we do help a good many cases, become less and less satisfied with our therapy in proportion to the number of cases we have seen.

—LEWIS WEBB HILL

CHAPTER XVII

DISCUSSION WITH THE PATIENT

This section might be termed "history of the present illness" but so much more information must be obtained than in routine histories that the above title becomes more appropriate.

To be serviceable the allergic history must be painstakingly obtained. There is little justification for the printed history blank in which answers are checked, yes or no. One is often astonished at the wealth of information in the past and family allergic histories, if the patient is given an opportunity to describe his experiences and is helped along with pertinent questions. The comprehensive history is not always necessary for adequate therapy, but is essential for clearest understanding of the patient's illness and a clearer understanding of allergy.

Illustrative case.—A striking example of the wealth of available information which may be overlooked as a result of haste, is the following personal experience.

A medical student came in on a Saturday morning when we were hurriedly attempting to finish up the work of the week. He had but a few hours in Richmond. Owing to the circumstances, the history of his present illness was but a short paragraph in the record. He was recorded as a case of intermittent urticaria and angioneurotic edema without clear

cut seasonal variation, and of several years' duration. He reacted to tomato and egg and was told to avoid these. A few months later he reported that he had been entirely relieved. This was, therefore, an allergic case sensitized to two foods, relieved on avoidance.

The record would have been closed at that, were it not that he spent the following summer working in my office. One day at luncheon, with plenty of time to sit and chat, he told me of his experiences. His turned out to be as unusual a case as one sees.

The first of his series of ailments became manifest in 1925 when he developed a severe acute right-sided abdominal pain of two days' duration. The white count remained normal, the temperature subnormal and the pulse slow. While the disease appeared to be a subacute appendicitis, the picture was not sufficiently clear to justify operation, and he was treated expectantly, with ice caps to the abdomen. Nausea persisted for some time following the acute attack, and the patient remained on a liquid diet for two months, losing twenty-five pounds in weight.

In October, 1927, he developed a persistent cough which lasted several weeks, with nasal symptoms suggesting a chronic sinusitis. X-ray examination of chest at that time showed some pleural thickening and dense lung markings on both sides which were interpreted as being suspicious of tuberculosis. Both conditions gradually improved.

In March, 1928, a hydrarthrosis appeared in the left knee with edema of the left foot and ankle. This was followed within twenty-four hours by involvement of the right ankle joint and the joints of the fingers. At this time the blood calcium level was found to be 9 mg. per 100 cc.; blood phosphorus 4.2 mg. The blood pressure was 118 systolic, 68 diastolic, and the hemocytologic findings were normal except for the presence of 4 per cent basophiles. The eosinophile count was 4 per cent. Temperature was subnormal, and the pulse slow. Intravenous typhoid vaccine gradually relieved the manifestations with entire recovery after two weeks.

In May of the same year he had a slight recurrence in the left knee, of short duration, which was this time accompanied by the appearance of yellowish red macules on the feet with rather diffuse reddening which gradually increased. The same discoloration soon appeared on the hands. There was apparently a general vasomotor instability of the extremities with associated profuse sweating. The extremities were painful. A diagnosis of erythromelalgia was made. During this attack the patient experienced vertigo when lying in bed with eyes closed, and when standing with eyes closed he fell to the left. Again he responded gradually to several intravenous injections of typhoid vaccine. The patient remained well for about six months, until November, 1928, when he again became acutely ill with cyanosis and paresthesias below the elbows and knees, hydrarthrosis of the right knee, and herpes on the right foot. Once again he responded fairly satisfactorily to intravenous shock therapy. At the end of the same month he suffered a recurrence of vertigo with the peripheral vasomotor manifestations which did not respond to pituitrin injections, responded only temporarily to adrenalin, and cleared up after an injection of typhoid vaccine intravenously. In ensuing months he had pleurisy with friction rub and an intrapulmonary shadow on x-ray, both of which promptly disappeared after adrenalin injections, "acute sinusitis" and meningismus with paralysis of the left arm, nystagmus and partial blindness likewise relieved by adrenalin. Later he had an obstruction of the urethra which required catheterization, and this again was relieved with adrenalin. Roentgenograms of the genitourinary tract showed no abnormal findings. On several occasions the patient experienced attacks of urinary frequency and urgency without polyuria. Several recurrences of sinus symptoms were sufficiently severe to require puncture of the antra, the fluid obtained always being serous. Mild attacks of vertigo became frequent, with the tendency usually to fall to the right. I had first tested him in July, 1929. Several trials of tomatoes in the autumn of 1929 caused recurrence of peripheral manifestations in the extremities. The eating of eggs in October of the same year produced an attack of angioneurotic edema involving the left eyelid, with an attack of croup and associated edema of the larynx. These symptoms returned again in March, 1930, following the inadvertent eating of eggs in mayonnaise. Toward the end of March he had one last attack of angioneurotic edema involving the face, this time while following his diet carefully. It was during the school examinations and may have been primarily neurogenic, although the patient himself suspected that milk to which he had given only a borderline reaction might have been responsible. In this connection it is of interest that cheese causes itching of the roof of the mouth.

In 1933 he reported that he had outgrown his sensitization to tomatoes but still had to be careful about eggs.

The point of interest is the pleomorphism of the allergic manifestations and their close resemblance to those of certain other clearly defined diseases. Cases of Ménière's disease have been described as of allergic origin; other cases apparently allergic have manifested intermittent hydrarthrosis; abdominal allergy is not uncommon; peripheral nerve palsy has been described as accompanying Quinke's edema; visual disturbances have been mentioned; and the symptoms of kidney colic have been traced to allergy in individual cases. But it appears rare indeed to find such protean manifestations in a single individual, due to only two etiologic factors.

This patient has manifested meningismus with generalized cephalic pain as severe as that of true meningitis, accompanied by peripheral nerve manifestations and probably due to an attack of angioneurotic edema in the brain substance; several attacks of clear-cut Ménière's disease; intermittent hydrarthrosis; amblyopia; nystagmus; symptoms almost indistinguishable from acute appendicitis; Dietl's crisis; urethral obstruction; intermittent bladder irritability; urticaria; erythromelalgia; peripheral nerve palsy; acute "sinusitis"; laryngitis; croup; and edema of the pulmonary tissues giving an x-ray picture suggestive of tuberculous involvement which promptly disappeared after adrenalin administration.

When we consider the pathology of angioneurotic edema, it seems surprising that this pleomorphic response is not encountered more frequently. It may well be that more painstaking analysis of patients' past histories will disclose that this observation is not as uncommon as it appears.

The history of other allergic manifestations did not help much in this case, since there was no personal history of other outspoken allergy such as hay fever, vasomotor rhinitis, or asthma or other disease frequently associated with allergy such as migrainous type of headache, colitis, or eczema, and the only family history that might possibly have been considered allergic was that of eczema in one sister and in the maternal grandmother.

The inference to be drawn is that allergy should be considered as a possible etiologic factor in the various individual disease pictures listed above and that the absence of a definite personal or family allergic history must not be accepted as ruling out such a possibility.

Following this experience I concluded that the best way to obtain an adequate allergic history is to take the patient out to lunch! Since then on more than one occasion I have put this into practice, especially with patients who have been through the usual routine but have not been relieved. It is always surprising how much additional information can be obtained when one is not hurried.

Customary routine.—The preliminary interrogation should establish the presence or absence of the outspoken allergic manifestations; asthma, hay fever, in or out of season, urticaria, eczema, periodic headache or migraine, indigestion associated with the eating of specific foods, food upsets or idiosyncrasy, and drug idiosyncrasy. These should be searched for in the present and past history and in the medical history of relatives and offspring. History of previous serum and vaccine treatment should be recorded, dates being compared with dates of onset of allergic symptoms. Both negative and positive information should be recorded, since for subsequent studies it is often as important to know which of the allergic group of diseases an individual has not had as it is to know what he has had.

Nasal allergy.—This includes much more than seasonal hay fever. A person may deny hay fever but admit that he sneezes many times in succession after arising in the morning. This is rather an important question since some-

times it is the only one which elicits a history of nasal allergy. Many will, on questioning, recall that they sneeze under certain circumstances during the day such as when powdering the nose, entering room filled with tobacco smoke, brushing the dog, when frying food, etc. Such experiences give a lead in the search for etiologic agents.

A woman complained of urticaria. Nothing in her history gave a clear lead as to etiology except that she sneezes when arising and when she enters the breakfast room. This appeared to have no association with her urticaria. Further conversation developed that the kitchen was warm, the breakfast room usually cool. More questioning developed that she also sneezes in air-conditioned "movies" in the summertime. Skin tests showed no cause for her urticaria. On account of her history of reflex sneezing she was tested for cold sensitization. This promptly induced urticaria. Physical allergy was suspected from a symptom which she had not associated with her complaint and which she would not have mentioned had not the questioning reminded her of it.

Only one with a hyperesthetic nose, usually allergic, can regularly produce a barrage of sneezes, separated only by the time necessary to take another breath. If a patient experiences this at any time of day or year, we may take it as presumptive confirmation of an allergic state.

In the same way, response to sudden atmospheric changes often gives a lead. Some sneeze on exposure to cold, others to heat, as entering a warm house in the winter time, or from exposure to strong winds or bright sunlight. Sneezing is not the only symptom. Nasal blockage and rhinorrhea must be considered. Asthma may occur, or merely fits of coughing. Urticaria is a rather frequent manifestation of physical allergy and is followed rather closely by angioneurotic edema, especially of exposed parts.

Many cases of so-called sinusitis are in reality nasal allergy. When the complaint is of sinus trouble one should learn whether symptoms are intermittent or seasonal, whether x-rays have shown evidence of sinus infection, whether local treatment has given relief, whether there is associated sneezing or rhinorrhea, and whether there is history of other allergic symptoms leading one to suspect that the "sinus trouble" is due in whole or in part to allergy.

TABLE XV. FREQUENCY OF "HEAD COLDS" AMONG 281 ALLERGICS AND 161 NONALLERGICS

	ALLERGICS		NONALLERGICS	
	NUMBER	PER CENT	NUMBER	PER CENT
Not susceptible	190	67.6	120	74.5
1-3 per year	45	16.0	26	16.1
4-6 per year	20	7.1	8	5.0
8-12 per year	3	1.1	0	0.0
"Frequent"	11	4.0	4	2.5
"Chronic"	12	4.0	3	1.8

Two thirds of allergies and three-fourths of nonallergies are not subject to "head colds." The difference is not great. About 9 per cent of nonallergies have more than 3 "head colds" per year, as contrasted with 16 per cent of allergies. Among the latter, many attacks may be of allergic coryza.

One should bear in mind that in food allergy the shock tissue may be in the nose. Not infrequently a patient will remark that he has attacks of sneezing after eating or drinking some specified food.

In clear-cut seasonal hay fever it is important to establish as clearly as possible the dates of onset and offset of symptoms. This is compared with the examiner's knowledge of the dates of pollination of the various allergenic plants. In most parts of the United States ragweed pollinosis commences after the middle of August. If a person complains of hay fever commencing the first

of August one must search for other offending pollens. In such a case the writer found that goldenrod was the offender. The interesting point was that for the preceding four years she had been treated with ragweed extract, always without relief. Her hay fever lasted through the ragweed season but it began too early.

Persons allergic to tree pollens are usually sensitized to more than one. Here it is especially important to know dates of pollination. A man had hay fever toward the end of February. He reacted to the pollens of maple, elm, oak and birch. Maple and elm were pollinating at the time, oak and birch were not due to pollinate for another four to six weeks. Coseasonal treatment was given with elm and maple pollen only. Six weeks later, when symptoms recurred, only birch and oak pollen were used.

Although the onset of ragweed pollination varies little from year to year, this is not true of trees or grasses. The length and severity of the winter materially influence the blooming of early flora, especially trees. Therefore, one cannot use an average-date-of-pollination chart for the trees, but must actually watch the trees come into bloom.

When the patient has a curious idea as to the cause of his nasal allergy, or other allergic manifestation, one should not categorically deny the possibility. There was a time when we believed that brightly flowering plants do not cause pollinosis. These possess sticky pollen, carried from plant to plant by insects. Only the wind-borne pollens produce pollinosis.

On the contrary, I find that many pollinosis victims, especially those allergic to the compositae such as ragweed, also react to the pollens of some flowers, as daisy, goldenrod, chrysanthemum, sunflower, dandelion, rose.

In one survey, for 100 persons allergic to short ragweed, Vaughan found 32 sensitized to sunflower, 2 to dahlia, 24 to yellow daisy, 30 to goldenrod, 22 to dandelion, 18 to rose, 2 to privet, 1 to apple. In a later series Grubb and Vaughan found for 100 persons allergic to short ragweed, 25 sensitized to sunflower, 31 to daisy, 42 to goldenrod, 25 to dandelion, and 19 to rose.

A woman with late summer hay fever reacted to chrysanthemum. Her neighbor raises chrysanthemums for sale. A child had hay fever in May, chiefly at night, and much more when sleeping in a room on the east side of the house. His mother suspected mimosa tree, in bloom outside the east window. Although mimosa pollen is entomophilous and not carried far on the wind, we established mimosa as the cause.

It is true that most pollinosis is due to wind-borne pollen. But we have found that attacks, usually of short duration, are sometimes due to the pollens of decorative flowers. Usually they occur in rooms containing flowers or in flower gardens. It is therefore important to listen to the patient's own suspicions and to follow up with testing or other studies. I suspect that often, when a physician reports a case of sensitization to some new or unusual substance, it has been the patient who has given the doctor the lead. The doctor had sufficient interest to investigate the possibility.

One not infrequently obtains a history of previous hay fever or perennial rhinitis, with no trouble within recent years. It is, therefore, important to obtain the past history of nasal allergy.

A woman with epilepsy gave no allergic history other than that up to five years before the examination she had had fall hay fever. With this historical background she was tested with several pollens. She reacted strongly to ragweed. Shown, thus, to be allergic, she was tested with foods, reacting to chocolate, orange, peanut and certain seafoods. She was placed on food avoidances.

She had been unable to leave the house without a companion because of the danger of an attack in the street. In the ensuing five years she has not had a single epileptic seizure and travels about the country, has even been to Europe alone on two occasions. She now eats seafood but continues to avoid the others.

Asthma.—Much of what has been said concerning nasal allergy applies in asthma. The history of previous attacks, age of onset, seasonal occurrence or otherwise, duration of attacks and of intervals of freedom should all be established. A composite of the information thus obtained often gives an excellent lead to the possible offending agent.

With asthma, as with hay fever, it is important to know when symptoms start and stop, and when they are more pronounced. Asthma may be due to pollens, in which case the incidence is seasonal; and it is important to know the date of onset and just when the season is over. Asthma, restricted to the summer months, is practically certain to be due to pollen. Asthma due to house dust and to foods is quite likely to be definitely worse in winter and better in summer. In fact, there are many patients, more particularly children, whose asthma is due to food, who remain well or nearly so throughout the dry, warm, weather of mid-summer to resume their asthma with the onset of changeable weather in the fall, in spite of the fact that they use the food to which they are sensitive through the summer just as in the winter months. Weather conditions appear to be responsible for this variation. In our experience, it is a mistake to assume that asthma which comes on in the fall months recurs through the winter and spring to clear up during the summer, is "intrinsic" asthma, or is due to infection of the respiratory tract, or is a manifestation of physical allergy and dependent upon cold. Asthma restricted to the summer months is almost always due to pollen, but asthma recurring only through the fall, winter, and spring may be due to many things. In some parts of the southern United States it may be due to the pollen of *Juniperus sabinoides* which blooms in midwinter or to *Ulmus americana* which blooms as early as late January or early February.

The time of day at which symptoms are more pronounced may be of importance. Some are worse during the day, but most patients are definitely worse at night. Nocturnal asthma does not indicate a sensitivity to some substance in the bedroom or about the bed. Apparently there are other factors which determine that patients are usually worse at night. The most common time for an attack to appear is at two or three o'clock in the morning. Many patients will go through the day with no dyspnea, and be waked with a sharp attack in the "small hours" of the morning. Many of these patients have their asthma from some food which they may have eaten during the preceding day or from house dust. They do not develop symptoms immediately on contact with the offending substance, but their attack occurs coincident with, and possibly because of, the meteorological changes which are most pronounced at that time. It seems probable that these patients are only moderately sensitive to their respective allergens and, when the temperature and barometric pressure are up and the humidity down, have no demonstrable symptoms. With the reversal of these conditions at night an attack ensues. That the weather conditions are not the prime factor is shown by the fact that, if the allergens to which the patient is sensitive can be avoided, then attacks do not recur in spite of marked variations in meteorological conditions.

A considerable number of patients will cough and become dyspneic as soon as they lie down. This can be shown not to depend upon the presence of feathers or other allergens, but to the change in position which the patient assumes.

Patients who are very sensitive may show symptoms promptly upon exposure to the appropriate allergen. This certainly is true of the pollens and animal emanations. It may result also from some occupational dusts. The association of the attacks with the working hours and conditions may be of great help in determining the cause of the asthma.

Patients frequently state that their first attacks of asthma followed closely upon a respiratory infection. Parents often state that the child's first attack was ushered in by an attack of some one of the "diseases of childhood." This does not mean that the asthma is infectious in origin, but only that the infection, in some unknown manner, brought about such a change in the patient that he became clinically allergic. The allergen to which he becomes sensitive may be wholly unrelated to the infectious process.

The same statement may be made about patients who relate their attacks of asthma to coincident attacks of upper respiratory infections, particularly "head colds." The statement may be made that asthma occurs only when the patient has a "cold." Often this is true, but often it means only that the patient is sensitive to some allergen wholly unrelated to the infection, and the "cold" acts as a "trigger" mechanism to set off the attack. This may be shown by the fact that the patient may clear up completely by avoidance of the allergen to which he is sensitive, though continuing to have recurring colds. There may be attacks of asthma which are entirely infectious in origin, but the coincident occurrence of asthma with colds does not justify the assumption. It should be remembered, too, that many persons have nasal symptoms ushering in the asthmatic attack which symptoms they believe to be due to a "cold" when, as a matter of fact, they may be entirely due to a nasal allergy. Fever often accompanies asthma in infancy and childhood, leading to an erroneous diagnosis of bronchitis or even of pneumonia. Many cases of croup are actually allergic. They are not necessarily errors in diagnosis. Croup appears sometimes to be an allergic manifestation.

Rackemann's classification of asthmatics into intrinsic and extrinsic is helpful. The extrinsic case is sensitized to some agent of exogenous origin. Symptoms occur only following contact with the agent. Between attacks the patient is free from symptoms. The intrinsic allergic is less frequently symptom free. This is the type in which bacterial infection appears to play a part; possibly also endocrine or other factors. The cause appears to come from within the body rather than from without. In my experience there are very few pure intrinsic allergies. We see many extrinsic cases and a large number of combined, where extrinsic factors play a part but the patient appears to be influenced by intrinsic factors also.

TABLE XVI. INCIDENCE OF HISTORY OF CROUP IN CHILDHOOD

STATUS	NUMBER QUESTIONED	POSITIVE HISTORY	PER CENT
Major allergic	44	19	34.5
Minor allergic	244	72	29.5
Nonallergic	160	28	17.5

Croup is not necessarily an allergic disease. However, in the writer's experience many cases are associated with allergy, particularly food allergy. The above table indicates that this disease may occur in nonallergies but that it is approximately twice as frequent among allergies.

Occasionally we see what appear to be pure intrinsic allergies, especially in asthma and urticaria. This is the chronic asthmatic without positive skin reactions, unless perchance to bacteria. This is the type who is usually taking large doses of adrenalin at frequent intervals, and one cannot be certain that the absence of skin reactions is not due to the constant use of adrenalin.

The duration of the individual attacks is influenced by two chief factors. Short exposure to the allergen, with avoidance at about the onset, will, as a rule, result in an attack of short duration. If asthma persists for many days, two causes must be suspected: (a) infection and (b) continued contact with the excitant. One looks especially for sensitization to agents which may be found on the bed or in the bedroom. Sometimes agents just outside the room are responsible. A woman who had been in bed with asthma for months was found allergic to feathers. Her husband was a pigeon fancier and one of the favorite roosts was the bedroom window-sill. The avoidance of feather pillows had failed because of the birds.

Asthma is not the sole allergic manifestation in the lower respiratory tract. I have seen several cases of "chronic bronchitis," usually with a nonproductive cough, due to food or inhalant allergy. Therefore, cases of simple bronchitis may be studied as possibly allergic, especially when there are other symptoms suggestive of allergy. A man had been subject to winter bronchitis for a number of years. He had an associated postnasal catarrh which always became worse with exacerbations of his bronchitis. There was very little sputum. Symptoms were worse at night but persisted through the day. The only outstanding point in his allergic history was that whenever he ate beef he had indigestion. He reacted to beef and several other foods, also to feathers and house dust. Dietary restrictions, the covering of his feather pillows with dust-proof slips, and feather and dust hyposensitization resulted in 80 to 90 per cent relief from his cough and catarrh.

TABLE XVII. ASTHMA AND HAY FEVER DETAIL

A reference outline of points worthy of consideration.

Name-----	Date-----
<i>Identification</i>	Face powder
Asthma	Odors
Bronchitis	Perfumes
Croup	Soap
Pneumonia	Crowds
Hay fever	Theatres
Sneezing	Coryza
Colds	Drugs
Coughs	Animals
Wheezing	Pets
Nasal obstruction	Furs
Stuffiness	Bedding
Sinus trouble	Catamenia
Itching palate	Exhaustion
Itching eyes	Shock
Itching nose	Specific localities
Itching throat	Change of locality
Itching ears	Constipation
Itching larynx	
Lachrymation	<i>Foods</i>
Olfactory impairment	Suspects
Taste impairment	Symptoms
Diurnal variations	Dislikes
	Symptoms

TABLE XVII.—CONT'D

<i>Associated conditions</i>	Cravings		
Eczema	Combinations		
Urticaria	Overeating		
Pruritus	Previous diets		
Other eruptions	Results		
Headaches	<i>Climatic</i>		
Migraine	Season		
Food upsets	Altitude		
Ivy poisoning	Temperature		
Urinary frequency	Humidity		
Asthenia	Wind direction		
Hypotension	Light		
Colitis	Specific localities		
Epilepsy			
<i>Family History</i>	<i>Bed room</i>		
Asthma	Always same room		
Hay fever	Attacks elsewhere		
Rhinitis	Sleep alone		
Urticaria	Room alone		
Eczema	Pillow		
Skin disease	Mattress		
Headaches	Covers		
Migraine	Wall coverings		
Food upsets	Rugs		
Colitis	Pets		
Ivy poisoning	Ventilation		
Hypotension	Plants		
Epilepsy			
<i>Contributing factors</i>	<i>Home</i>		
Chilling	Describe house		
Electric fan	Time living there		
Draughts	Heating plant		
Dust	Dust		
Smoke	Cleaning methods		
Tobacco	Suspect rooms		
Flowers	Pets		
<i>Grounds</i>	Mice		
Flowers	Flowers, etc.		
Weeds	Factories		
Pets	Smokes		
Live stock	Odors		
Contents of barn	<i>Occupation</i>		
<i>Neighborhood</i>	Detail		
Time living there	Contacts		
Other cases	Ventilation		
Their causes	Dusts		
Trees	Flowers		
Plants			
Fields	<i>Miscellaneous</i>		
Weeds	X-ray chest		
Insects, etc.	X-ray sinuses		
	Other x-rays		
	Gastric analysis		
	Remedies tried and results		
<i>Nose and Throat Operations</i>			
Operation	Date	Reason	Result
1.			
2.			
3.			
4.			
<i>Remarks:</i>			

I have seen true pulmonary edema occur in a decompensated cardiac, the attacks being initiated by exposure to inhalant or ingested allergens. A hypertensive woman experienced true attacks of acute pulmonary edema each time she went into a certain movie house in her city. She could go to other theaters without trouble. She had similar episodes each time she ate eggs. Avoidance of the specified theater and eggs relieved the attacks of pulmonary edema although she eventually died a cardiac death. At no time during her life did she have true asthma.

The history of response to medication is sometimes of importance in asthma as well as in hay fever and other allergic symptoms. A woman had had ragweed hay fever for years. Her rhinologist had given her a spray containing cocaine. This she had used each ragweed season with considerable relief but in the 1936 season her symptoms were much worse. We found her sensitized to ragweed, house dust and a few other allergens. Treatment, however, gave very little relief. Following the 1936 ragweed season, for the first time, symptoms did not clear up. They continued through the winter, until, in February, we suspected the possibility of sensitization to the cocaine spray which she was still using. After five days' avoidance she was practically symptom free.

The foregoing detail of suggested lines of questioning in a case of inhalant allergy indicates the general character of the discussion with the patient. Not every one of these leads need be followed in the preliminary discussion, but before the case has been completed all pertinent observations suggested by this detail should have been followed up.

Contact dermatitis.—No matter what the allergic manifestation of the moment, it is not unusual to obtain a history of eczema in childhood, especially facial eczema.

Infantile eczema usually clears up after a time, due to automatic cessation of contact with offending substances or for other reasons. However, it should be inquired for in the history. It may be due to contact, foods or inhalants.

The location or distribution of dermatitis is often of significance. Contact eczema, from substances which come in touch with the skin, is usually distributed in exposed areas such as the hands, face, neck and ankles. In the case of soaps, powders, dyes, articles of clothing, deodorants and occasional other factors, the dermatitis may be entirely or chiefly limited to the covered surfaces. If contact has been sufficiently intense or prolonged, the lesion is likely to be exudative. If, therefore, a dermatitis is limited to exposed surfaces or is vesiculated or "weeping," history of exposure to contact allergens should be investigated. Many contact dermatoses are occupational in origin. Such apparently nonallergenic substances as wood, sawdust, paper, metals (for example, nickel plated jewelry), rubber and the like may be responsible. The patient's occupational exposures should be investigated. Sometimes contact dermatitis shows a seasonal variation or other regular or irregular periodicity which aids in the search for the cause. A physician experienced a contact type of dermatitis on his face, hands and around his ankles, following golfing and hunting. He had it at no other time. Golfing early in the season caused no trouble. A curious feature of his hunting experience was that the dermatitis at that time was always worse on the right cheek. He was found allergic to ragweed oil, accounting for his experience while golfing, and gun oil with which he customarily polished the gun and which was soon transferred during use to his right cheek.

Immediate environmental contact factors should be sought. A physician with contact eczema of the forehead and hands was found sensitized to leather and was relieved following avoidance of gloves and the substitution of a cloth

hat band. A year later the hand lesions returned. This disturbed him for some time, until he realized that the cause lay in the leather grips of his golf clubs. He wrapped these with adhesive, with consequent cure.

A physician with dermatitis of the flexor surfaces of the fingers of the left hand searched the etiologic factor for many months before he realized that a leather grip wrapped around the steering wheel of his car might be the excitant. Removal of the grip resulted in cure. Many months later he found a similar lesion on the right hand only. Again it took some time before he realized that the leather key holder in his right hand trousers pocket was the excitant.

TABLE XVIII.—INCIDENCE OF HISTORY OF RHUS DERMATITIS IN A COMMUNITY OF 508 PERSONS (ALL AGES)

GROUP	NUMBER	HISTORY OF IVY POISONING	PER CENT OF GROUPS
Nonallergic	159	42	26.5
Major allergic	54	15	28.0
Major and minor allergic	299	99	33.0

50 cases in whom designation as between "minor allergy" or "no allergy" was uncertain, are not included.

The incidence of ivy poisoning is almost as high in nonallergics as in allergies. Since this appears to be an allergic disease this again indicates that the difference between allergies and nonallergics is primarily only quantitative.

Rhus dermatitis, due to rhus toxicodendron, poison ivy in the eastern portion of the country, poison oak in the Far West, is a typical contact type of dermatitis. Usually the seasonal recurrence and the history of possible exposure aid greatly. It is characteristic of rhus dermatitis that, although starting on exposed surfaces, it often spreads to other areas, especially the genitalia in the male, the contact agent having been carried on the fingers.

Oils of plants other than poison ivy, poison oak, sumac and primula may cause dermatitis quite indistinguishable from true rhus dermatitis. As a rule prolonged or chronic exposure is necessary, much more than in rhus sensitization. As a consequence plant dermatitis is seen especially in florists and farmers.

One reason for the insistence by some investigators that there must be a fundamental difference between experimental anaphylaxis and clinical allergy is the apparent fact that symptoms may occur on first contact, without an earlier sensitizing exposure. Every allergist is confronted with apparent examples of this sort. The mother insists unequivocally that the child's first allergic symptom appeared the first time the child ever ate a certain food. Occasionally this may be true, the child having been sensitized in utero after the mother had eaten the food, but much more often I believe the true fact to be that memory is fallacious. In contact dermatitis especially, the physician is often assured that symptoms occurred indubitably following first contact. An adolescent boy was given a sample bottle of Aqua Velva as an after-shaving face lotion. He was known to be of allergic habitus, having previously had infantile eczema, childhood eczema, asthma and perennial vasomotor rhinitis. About three weeks later he had a diffuse, dry scaling facial dermatitis. Aqua Velva was suspected. He had had the dermatitis one week and insisted that he had used the lotion for but one week. On further questioning he did recall that when it was first given to him he had used it one or two mornings and then had forgotten it during the two week interval. Had several weeks or months elapsed between his experience and the interrogatory, he would probably have remained convinced that symptoms began within a day or two after first contact.

Contact dermatitis due to occupational exposure can be shown to require an "incubation period." The patient does not develop symptoms for a variable period after beginning his contact. Contact dermatitis from drugs can usually be shown to require this same incubation period if the taking of the history is detailed and painstaking enough.



Fig. 17.—Atopic dermatitis. Flexor surfaces are predominantly involved, in the elbows, axillae, popliteal space, and neck. There is no weeping except secondary to scratching.

Atopic dermatitis. Chronic dermatitis may develop after the ingestion or inhalation of allergenic substances which are carried through the blood to the skin. In this case the lesion is deeper, and classically, presents a different distribution. It does not exude or weep nor does it vesiculate. The only serous exudation that accompanies it is that which may follow trauma of scratching, with or without secondary infection.

The lesion is distributed on the flexor surfaces, the antecubital fossae, the popliteal spaces, the wrists, the flexor surfaces of the neck, and the face. It may occur under the breasts and may spread rather widely from these original locations. There may be some exfoliation, more characteristically lichenification or thickening of the skin as a protective measure, but as stated above there is rarely weeping and none of the type characteristic of contact dermatitis. Pruritus is often pronounced. Both types of allergic dermatitis may occur in the same individual.

Ingested food, inhaled house dust, feathers, silk dust or other chronic inhalant factors may be important etiologic agents. Once the inhaled substance enters the blood through the lungs, it may be as allergenically active as the ingested substance which enters the blood through the intestinal tract.

This form of dermatitis has had many names, the most recent in general use being "*neurodermatitis*." Sulzberger has discussed the inappropriateness of the term and suggested atopic dermatitis as a designation distinguishing the lesion from contact dermatitis. Since both forms are allergic, and the latter



Fig. 18.—Involvement of flexor surfaces in atopic dermatitis due to inhalation of house dust. This patient was also allergic to some foods, but did not clear up adequately until hypo-sensitized with dust extract.

term could be applied equally well to either, the writer feels that Sulzberger's designation is most acceptable. One might object to the term dermatitis, preferring *dermatosis*. The present concept is that the suffix *-itis* indicates an inflammatory response associated with bacterial infection and that *-osis* designates a lesion in which the reaction to bacterial infection does not play a part.

Atopic dermatitis occurs more frequently in childhood and often clears up at or shortly after adolescence, but may occur at any age.

Food idiosyncrasy.—This may commence at any age. The patient should be interrogated concerning any foods that upset or disagree with him and the nature of the resulting symptoms. These may involve any of the shock tissues, but the patient is more likely to have noticed a cause-and-effect relationship

if symptoms are gastrointestinal. Other symptoms such as migraine or urticaria are less often associated in the patient's mind with food etiology, unless symptoms ensue quite soon after ingestion, and unless the food is one which he indulges in only occasionally or at intervals. It is unusual for a patient to volunteer that a staple food is responsible for symptoms.



Fig. 19.—Detail of the lesion of atopic dermatitis or neurodermatitis at the end of the elbow. Note absence of weeping and beginning lichenification.

Often one forgets that some food infrequently eaten causes symptoms, but will recall the fact if the specific food is mentioned to him. Since this would be a time-consuming procedure, the same end is accomplished by having the patient fill out the questionnaire which appears at the end of this chapter, in which the foods customarily eaten are listed.

The patient will not infrequently give a history of having experienced an idiosyncrasy to a certain food in the past but from which he appears to have recovered at the time of study. As with pollens, this should be recorded in the anamnesis.

There are many foods which one will suspect as causing trouble but concerning which there is uncertainty. There should be recorded as such, for future comparison with the results of testing and for future trial by the individual. Obviously not every suspected food will be found to cause symptoms. This is also true with many foods which give positive skin reactions.

It is especially in food allergy that the bizarre symptoms are recorded. This includes renal colic, bladder irritability, childhood nocturia, angioneurotic edema, recurrent neuritis, transient palsy and blindness, erythromelalgia, erythema multiforme, conjunctival chemosis, purpura, intermittent hydrarthrosis, etc. There is no curious or unusual symptom which the patient may suspect as attributable to specified foods which does not deserve careful allergic investigation.

Formerly, foods were eaten in season much more than they are today. Thirty years ago oranges were available only at certain times of the year. Today they may be had at any time. With modern rapid refrigerated freight transportation the average American dietary is far less subject to seasonal influence. Furthermore, many foods eaten fresh only during certain months may be had, preserved, through the year. Nevertheless, there is some seasonal fluctuation, justifying the interrogator's interest in annual variation of symptoms. Melons,

frequently allergenic, are possibly the most outstanding example. When symptoms always occur after Thanksgiving and Christmas, even though they also appear at other times, turkey, cranberries, chestnuts and the other appurtenances of these feast days should be held under suspicion. The occurrence of symptoms chiefly on Friday or Saturday often suggests seafoods.

Check List for Foods

Check the foods on this list that you have been eating.

Triple check (xxx) for foods eaten daily or at least several times weekly.

Double check (xx) those eaten occasionally, as once weekly.

Single check (x) those eaten rarely, less than once weekly.

<i>Foods</i>	<i>Foods</i>	<i>Foods</i>	<i>Foods</i>
1. Walnut	Celery	Coconut	26. Chicken
Pecan	Parsnip	Date	27. Pork
Hickory	Carrot	Pineapple	Ham
Butternut	Dill	Hazelnut	Bacon
2. Swiss chard	11. Sweet potato	Filbert	28. Lamb
Beet	Yam	Chestnut	Mutton
Spinach	12. Tomato	Pistachio	29. Duck
3. Radish	Irish potato	Currant	Goose
Turnip	Egg plant	Gooseberry	Turkey
Cabbage	Green pepper	Huckleberry	Other Fowl
Cauliflower	Red pepper	Blueberry	30. Shad
Brussels sprouts	Ground cherry	Cranberry	Shad roe
Broccoli	Pimento	Olive	Bass
Kale	13. Pumpkin	Olive oil	Chub
Turnip salad	Squash	Wesson oil	Pike
Kohl-rabi	Cantaloupe	Mazola oil	Herring
Watercress	Cucumber	Tea	Salmon
Rutabaga	Watermelon	Coffee	Tuna
Mustard	Muskmelon	Beer	Perch
4. Blackberry	Honey dew	Wines (specify)	Croaker
Strawberry	Casaba	Distilled beverages	Codfish
Raspberry	Pickles	(specify)	Trout
Apple	14. Lettuce	Soft drinks	Butterfish
Pear	Artichoke	(specify)	Mackerel
5. Almond	Endive	Coca-Cola	Sardine
Cherry	Salsify	Yeast	Anchovy
Apricot	Oyster plant	Maple Syrup	Caviar
Plum	Chickory	Maple Sugar	Spot
Peach	15. Wheat	Molasses	Swordfish
Prune	16. Rye	Sorghum	Sole
6. Green pea	17. Barley	Cinnamon	31. Lobster
Black-eye pea	18. Oat (Oatmeal)	Nutmeg	Crab
Lima bean	19. Rice	Vanilla	Shrimp
Butter bean	20. Corn (Hominy)	Mushroom	32. Clam
Kidney bean	21. Onion	Tapioca	Oyster
Navy bean	Garlic	Paprika	Scallops
Boston bean	Asparagus	23. Beef	33. Chewing gum
String bean	Leeks	Veal	Chewing tobacco
Snap bean	Chive	Liver	Medicines
Lentil	22. Banana	24. Milk	(specify)
Peanut	Ginger (-ale)	Cream	Hog lard
Honey	22a. Buckwheat	Butter	Crisco
7. Lemon	Rhubarb	Cheese	Snowdrift
Orange	22b. Mulberry	(specify)	Other shortening
Grapefruit	Fig	Oleomargarine	34. Any other
8. Grape (Raisin)		25. Eggs	beverage,
Okra (Gumbo)			food, drug,
9. Cocoa, chocolate			etc.
10. Parsley			

Beverages such as tea, coffee, Coca-Cola, ginger ale, Postum and alcoholic concoctions may be allergenic. Tea and coffee are fairly frequent offenders in my experience. The allergic individual should not indulge in proprietary mixtures the precise constituents of which are not known. Alcoholic beverages,



Fig. 20.—Involvement of the popliteal area in atopic dermatitis.



Fig. 21.—Involvement, primarily of the flexor surface, but due to occupational contact rather than ingestant or inhalant allergy.

even of the distilled varieties, may be specifically allergenic. A woman experienced urticaria each time following the drinking of Scotch whiskey. Rye, corn and gin caused no trouble. A man experienced nasal allergy after rye but not after Scotch, corn or gin. A man responded with hypertension to the ingestion of Martinis. Following Scotch his blood pressure regularly fell.



Fig. 22.—Contact dermatitis, in contrast to atopic eczema, shows no predilection for flexor surfaces, chiefly involving exposed areas such as hands, forearms, ankles, legs, and face. When acute, this lesion often exudes.

Fermented beverages, beer, ales and wines contain many potentially allergenic constituents such as cereal grains, malt, yeast and the fruit from which wines are made.

I know of no work that has shown that a person sensitized to barley will experience difficulty from a distilled liquor made from barley. The same applies to the other cereal grains, foods, etc., mentioned. However, I do know that such beverages will cause symptoms in the occasional case, irrespective of the original sources of the ingredients and it is, therefore, my custom to advise patients to avoid such beverages when they are found sensitized to any of the original ingredients.

Gastrointestinal allergy. What has been said in the preceding section applies equally here. As a rule allergic symptoms referable to the gastrointestinal tract are due to foods, but this is not always true. Drugs are rather frequent offenders. Gastrointestinal symptoms may even follow hypodermic medication.

The lips, the portal of the gastrointestinal tract, may be allergically responsive. The two commonest manifestations are angioneurotic edema, usually occurring very promptly after the ingestion of foods or drugs; and cheilitis such as occurs in women using allergenically active lipstick or in smokers sensitized to tobacco or one of the other constituents of tobacco products. Herpes labialis, especially the recurrent form, is not infrequently associated with food allergy. The same applies inside the mouth, to recurrent canker sores. Ratner has reported stomatitis from sensitization to dental plates. There was a diurnal variation elicited in the discussion with the patient, in that the sore mouth improves at night when the plate is not in the mouth. In stomatitis which might be allergic, questioning should cover those things which may enter the mouth at



Fig. 23.—Difficulties in differential diagnosis. Body involvement is chiefly of flexor surfaces but the involvement of the skin of the face and neck, stopping sharply at the collar line, indicates probable contact dermatitis. In such cases the lesion may be due entirely to contact, flexor distribution being due to warmth, moisture, and the nature of the contact substance, or both contact and atopic factors may be active. Atopic as well as contact studies are indicated (foods, inhalants, etc.).

any time. Besides foods and drugs we would mention dental powders and pastes, mouth washes, and chewing gum.

The classical allergic reaction in the stomach and intestines is either nausea and vomiting shortly after ingestion of the etiologic agent or, if it is retained, diarrhea or mucous colitis after an interval of several hours. Pain is frequent. In the discussion with the patient, attention should also be given to other rather more allergically obscure symptoms. Peptic ulcer, cholecystitis, and

appendicitis are in no sense primarily allergic diseases and in the vast majority of instances allergy undoubtedly plays no part whatsoever. However, one finds food for thought in some of the older writings on the dietary treatment of gall bladder disease. As recently as twenty years ago a gastroenterologist of international repute wrote concerning his recommended dietary proscriptions in this disease. It reads almost like an idiosyncrasy list of today. It lists especially those foods which any series of minor allergies will designate as most commonly causing allergic symptoms. The gastroenterologist also states that one characteristic of gall bladder disease which may be used in differential diagnosis is that the patient can usually name certain specific foods which bring on attacks.

The interesting fact is that these statements are quite true. A person with true gall bladder disease may experience exacerbation after eating foods to which he is allergic. Allergy is not responsible for the cholecystitis or the gall stones but the allergic state may color the symptomatology of the organic disease. Therefore, the allergic patient with bile tract disease may be aided symptomatically as a result of allergic study. The fact that there is other obvious etiology should not deter the physician from search for allergic excitants.

Why should the allergic reaction cause exacerbations in a nonallergic affection of this sort? Although no direct experimental evidence is available, two observations offer a plausible explanation. Auer applied xylol to the ears of nonsensitized rabbits. This caused no great degree of inflammation. He found that if xylol was applied to sensitized animals which were then given otherwise ineffective doses of antigen, local necrosis occurred in the areas treated with xylol. He concluded that the inflammatory action of xylol caused the accumulation of effective amounts of antigen in the locality affected. Valy Menkin later showed that foreign protein introduced into the circulation accumulates in an inflamed area, in greater concentration than in the normal tissues. These observations point toward the explanation that antigen becomes more concentrated in irritated or inflamed regions than elsewhere. It is easy to understand how the antigen-antibody reaction and the resultant allergic response might consequently be more pronounced in such regions. If this be true, such a local allergic reaction could be counted upon to result in a flare-up of the organic pathology.

Milligan has told the writer of a woman whose gastrointestinal symptoms were so characteristically those of gall stones that she was operated upon. After the operation, symptoms recurred and were ascribed to adhesions. These were broken up at a second operation. The attacks continued. Leukopenic index determination showed her allergic to coffee and orange. Since then, avoidance has relieved her and the taking of either has brought on symptoms indistinguishable from gall bladder disease.

A similar exacerbation after allergenic exposure appears possible in peptic ulcer. Kern and Stewart showed that allergies with ulcer were sometimes sensitized to milk and that dietary treatment was ineffective until after the usual ulcer diet with its milk base had been changed to one containing no milk or milk products. Lee Gay studied ulcer cases allergically, using skin tests, found a number allergic to certain foods and succeeded in relieving them by allergic dietary avoidance even though the customary ulcer therapy had, in some cases, failed to benefit. Harkavy has shown that the general run of ulcer cases is sensitized to tobacco in a higher percentage than the general run of normal individuals.

The writer has seen no cases of true acute appendicitis in which the attack was clearly initiated by contact with an allergenic food. I have seen allergies with symptomatology due to food allergy which was quite indistinguishable from that of appendicitis. McIntosh showed that in patients with characteristic history of appendicitis who were not relieved following appendectomy, microscopic study sometimes showed preponderance of eosinophiles in the wall of the appendix rather than the usual picture of bacterial inflammation. To this extent there is what we must consider appendiceal allergy, although much of it is without doubt associated with an allergic colitis.



Fig. 24.—An urticarial wheal on the ocular conjunctiva, occurring as an acute reaction after the eating of cucumbers. Wheat sometimes causes the same response, and sometimes spastic colitis in this case. The lesion always occurs in the left eye and is rarely accompanied by any other cutaneous or visible mucous membrane response. It clears up rapidly after the instillation of adrenalin eye drops.

From the lips to the anus allergy may color or dominate the picture of a variety of diseases.* Even perianal eczema or pruritus ani may be allergic. Terrell and Vaughan found that one-third of those with pruritus ani or perianal eczema in whom careful antecedent proctologic study had failed to show any definite etiology such as fungus infection, parasites, hemorrhoids, were relieved following allergic dietary avoidances.

Migraine.—Migraine is a symptom complex of which headache is the most outstanding. The classical description of migraine is seldom completely reproduced in the patient. One or more of the symptoms may be absent. It may, however, be diagnosed readily in most instances and differentiated from other headaches. It is a disease the episodes of which are initiated by a wide variety of causes, many of them nonallergic. There are those who believe that migraine occurs only in a certain type of person, and that its cure can be effected only by psychiatric means. Others believe them all to be allergic in origin. The truth probably lies somewhere between these extremes. Everyone working in the field of allergy has seen typical migraines which were cured by the removal of certain foods from the diet without any other therapeutic means. But it must be admitted that a large number of them will not respond to such measures and cannot be controlled by allergic management.

Not all allergic headaches present a picture of classical migraine. The absence of a typically migrainous character does not rule out allergy. Some of

* A woman with allergic spastic colitis develops constipation which lasts as long as a week after eating salad but more. She has regularity again on her in another instance, producing pronounced swelling of the abdomen, suggestive of a seven months' pregnancy. They also cause chemosis of the conjunctiva.

these are apparently primarily an allergy due to the localization of the reaction in the vessels of the meninges. Others are secondarily allergic in that the primary allergic reaction is in the mucosa of the nose and sinuses, and the headache results from the nasal and sinus blocking.

In discussing headaches with the patient one should inquire concerning etiologic suspects, especially occasional foods; age of onset, frequency, periodicity, relationship with endocrine disturbance such as adolescence, pregnancy, catamenia and menopause; and other excitants including worry, fatigue, gastrointestinal disturbance, constipation, emotional upsets, etc. One should attempt to determine whether the headache can be classed as true migraine. This is facilitated with the questionnaire at the end of this chapter.

Urticaria.—This is not invariably allergic. It may occur in endocrine disturbances, in association with focal infection, or in purely psychogenic states. All must be gone into thoroughly in the history. This is especially true with regard to the emotional make-up, sources of worry and the like. Duke has emphasized the emotional factor. The older writers, prior to the allergic concept, did so especially.

Usually one either finds the cause quickly and provides prompt relief, or, failing this, one finds the study and treatment long drawn out and often unsatisfactory. The allergist who realizes that nonallergic factors may be most important will accomplish relief in a higher proportion of his urticaria cases.

Examples of the importance of information on the emotional problems in urticaria are given in Chapter XVI. This may apply in other allergic diseases. It is often difficult to elicit this information because as a rule it deals with an emotional problem which in normal circumstances would place upon the victim the burden of silence. The patient must adjust himself to his environmental problem. Failing, he reacts with allergic symptoms. He is not likely to volunteer the information, because he sees no association between his problems and his skin manifestation.

Drug idiosyncrasy.—The most outstanding point in obtaining possible history of drug idiosyncrasy is that the majority of the American people are accustomed to drugging themselves with materials purchased "over the counter" without physician's prescription and that in an interrogatory they are apt to overlook the fact that they are taking drugs quite regularly. This applies especially to aspirin, the various laxatives, nose drops, ointments such as zinc oxide, hypnotics, and the proprietary analgesics. Time and again the allergist will receive a negative answer concerning "any drugs taken" which the patient readily rectifies if specific illustrations such as the above are mentioned.

The person with chronic or recurrent headache who procures a glass of effervescent headache powder at the soda fountain is likely to forget this is a drug.

Aspirin is a frequent cause of allergy. Most of the proprietary pain killers with secret formulae contain either aspirin or amidopyrin. Several cathartic ingredients are potentially allergenic, the most noteworthy of which is phenolphthalein. Since this is an efficacious laxative it appears in many proprietary formulae.

A woman with urticaria eventually traced the cause to belladonna in lapaetic cathartic pills. The most common form of reaction to drugs is some form of skin

eruption, but fever, adenopathy, leucocytosis, leucopenia, or albuminuria all may be found. Certain drugs are prone to produce certain types of eruption. Penicillin produces reactions which are frequently indistinguishable from serum reactions.

Biologicals.—We have seen that the majority of those who receive serum treatment become at least temporarily reactive to horse serum. Whenever it becomes necessary to give a preparation of this nature to an allergic it is important that a history be obtained concerning previous administrations of biologicals and whether there was any ensuing reaction, either immediate or delayed, in the form of serum sickness.

Incidental allergic symptomatology.—It is the rule rather than the exception, that the allergic has or has had more than one allergic manifestation and can be shown to be sensitized to more than one allergen. In the preceding paragraphs I have outlined the direction of the questioning of a patient with one or another of the more outstanding allergic expressions. The complaint may be single but if the discussion is carried far enough, usually one, often several other symptoms will be recognized in the past or present history. The discussion should include all phases in sufficient detail to be inclusive. Occasionally one will mention some curious unusual or bizarre symptom which might or might not be associated with allergy. In each instance it is worth the effort to investigate the curious and sometimes apparently silly suggestions of the patient concerning his or her illness. Many times the conclusion will be that allergy is not a factor, but sometimes it will be. In this way the unusual allergic manifestations have been discovered.

Family history.—The information gained here is usually only confirmatory, helping to establish a probable allergic etiology. Even here it is not of extreme value since the absence of a positive family history in no way invalidates the existence of allergy in the patient. However, the information acquired does provide background for the patient's history. Discussion of allergy in a relative will sometimes recall some forgotten symptom of childhood. As a rule, the heavier the allergic inheritance, the younger the patient will be when symptoms first appear. The manifestations will be more numerous and varied. The interrogation should include parents, grandparents, brothers, sisters, aunts, uncles and children.

Nonallergic conditions. The discussion should include a description of nonallergic conditions from which the patient has suffered, operations, etc. Sometimes the operations to which the patient has been subjected present a commentary on the failure of previous physicians to recognize the allergic state.

Allergy questionnaire.—Following the preliminary discussion the patient may fill out the following questionnaire. This has certain advantages. It is a time saver. It aids completeness. The patient can fill it out at his leisure when there is no feeling of hurry, thus favoring accuracy and thoroughness. I would emphasize that the questionnaire is not the history of the present illness but is to be used as supplementary thereto.

Idiosyncrasy List I

Your Name _____ Date _____

Nearly one-half of all persons find that one or more special foods disagree with them in one way or another. Have you, or have you had, any food idiosyncrasies? Are there any foods which you avoid because you have found from experience that they upset you in one way or

another? The following are symptoms often mentioned in this connection. Please write any such symptoms attributable to any one or more of the foods, on the accompanying check list. Write the symptom after the name of the food. Do not record symptoms unless you suspect or know from experience that certain definite foods cause them. If you have these symptoms but do not know any cause, do not record them.

Symptoms: Gas — Belching — Heartburn — Nausea — Vomiting — Cramps — Diarrhea — Colic — Colitis — Canker Sores (ulcers in mouth) — Sore Mouth — Gall bladder attacks — Indigestion — Chest pains — Headaches — Hives (nettle rash, urticaria) — Itching — Skin rash — Eczema — Swelling of skin (eyes, lips, etc.) — Bladder symptoms — any other symptom that you know is due to some definite food.

Please read the above list again, carefully, before filling in the answers. If you just *suspect* such and such a food, write the symptom and after it, put "suspect." Bear in mind that a food may cause symptoms only at times. That is, a food such as sweet potato may actually cause headaches, etc., but one may be able to eat it at times *without* headaches. In such a case you will probably *suspect* such a food, even though you don't actually *know* that it is causing trouble. But we are interested in knowing what foods you suspect, and why you suspect them, so that we can compare your suspicions with the food reactions obtained by testing.

Now (on the back of the check list, if necessary) go into as much detail as you can in describing just how those foods which you have checked affect you, how you discovered them, why you think they cause trouble, etc.

Note any other foods, not listed, that you have found to cause symptoms, such as "sausage, Brunswick stew, sweets, mayonnaise, etc." Note the symptoms.

Are there any *combinations of foods* such as "sea foods and cream; milk and fruit; orange juice and ice cream, etc.," which you think upset you? Describe attacks in detail (on back of sheet.)

If there are any foods that you dislike write "dislike" after them, and also write the reason why.

Finally, please read this sheet again, and review your answers very carefully and be sure you have explained them all in detail, since this is important in helping us to find *all* the causes of your allergy.

Name----- Date-----

<i>Foods</i>	<i>Foods</i>	<i>Foods</i>	<i>Foods</i>
Walnut	Celery	Coconut	Chicken
Pecan	Parsnip	Date	Pork
Hickory	Carrot	Pineapple	Ham
Butternut	Dill	Hazelnut	Bacon
Swiss chard	Sweet potato	Filbert	Lamb
Beet	Yam	Chestnut	Mutton
Spinach	Tomato	Pistachio	Duck
Radish	Irish potato	Currant	Goose
Turnip	Egg plant	Gooseberry	Turkey
Cabbage	Green pepper	Huckleberry	Other fowl
Cauliflower	Red pepper	Blueberry	Shad
Brussels sprouts	Ground cherry	Cranberry	Shad roe
Broccoli	Pimento	Olive	Bass
Kale	Pumpkin	Olive oil	Chub
Turnip salad	Squash	Wesson oil	Pike
Kohl-rabi	Cantaloupe	Mazola oil	Herring
Watercress	Cucumber	Tea	Salmon
Rutabaga	Watermelon	Coffee	Tuna
Mustard	Muskmelon	Beer	Perch
Blackberry	Honey dew	Wines (specify)	Croaker
Strawberry	Casaba	Distilled beverages	Codfish
Raspberry	Pickles	(specify)	Trout
Almond	Lettuce	Soft drinks (specify)	Butterfish
Cherry	Artichoke	Coca-Cola	Mackerel
Apricot	Endive	Yeast	Sardine
Plum	Salsify	Maple syrup	Anchovy
Peach	Oyster plant	Maple sugar	Caviar
Prune	Chickory	Molasses	Spot
Green pea	Wheat	Sorghum	Swordfish
Black-eye pea	Rye	Cinnamon	Sole
Lima bean	Barley	Nutmeg	Lobster
Butter bean	Oat (Oatmeal)	Vanilla	Crab
Kidney bean	Rice	Mushroom	Shrimp
Navy bean	Corn (Hominy)	Tapioca	Clam
Boston bean	Onion	Paprika	Oyster
String bean	Garlic	Beef	Scallops

<i>Foods</i>	<i>Foods</i>	<i>Foods</i>	<i>Foods</i>
Snap bean	Asparagus	Veal	Chewing gum
Lentil	Leeks	Liver	Chewing tobacco
Peanut	Chive	Milk	Medicines (specify)
Honey	Banana	Cream	Hog lard
Lemon	Ginger (-ale)	Butter	Crisco
Orange	Apple	Cheese (specify)	Snowdrift
Grapefruit	Pear	Oleomargarine	Other shortening
Grape (Raisin)	Buckwheat	Eggs	Any other
Okra (Gumbo)	Rhubarb		Beverage, food,
Cocoa, chocolate	Mulberry		Drug, etc.
Parsley	Fig		

Idiosyncrasy List II

Your Name _____ Date _____

Very many persons find that at one time or another in their lives they have certain symptoms following contact with certain extraneous substances. Often they find that these substances continue to cause trouble every time. Sometimes they cease to cause trouble after a few years, or they may cause trouble at certain times but not at others. Please record below any substances which you have found to cause symptoms mentioned below. Some of the more common causes mentioned by other patients are listed in parentheses for your aid. Describe in detail how they affect or affected you. Write down whether they no longer trouble you. If so, how long did they bother you? Please make your answers very explicit. Describe any other symptoms that you can attribute to some particular substance with which you come in contact. If you suspect certain things but cannot be sure, describe them and indicate that you just suspect them, and tell why you do.

Sneezing Attacks (Sneeze several times in succession): *Stuffy nose*: *Coughing*: *Asthma*.
(House dust — Hay — Tobacco smoke — Coal gas — Weeds — Grasses — Playing golf in springtime — Flowers — On arising from bed — Soap flakes — Soaps — Shaving soap — Washing powder — Face powder — Cosmetics — In crowds — At movies — In church — Wheat flour — Feathers — Flaxseed — Paints — Varnishes — Frying food — Wind — Heat — Strong light — Threshing grain — Smoke — Cats, dogs and other domestic animals, etc.)

Itching, Hives, Rash, Eczema: *Swelling of eyes, lips, etc.*

(Wheat flour — Rice powder — Corn shucks or stalks — Corn fodder — Straw — Hay — Oats — Grasses — Weeds — Grape Vines — Fuzzy vines — Peach skin — Vegetable skins — Snow-on-Mountain — Soaps and soap powders — Cosmetics — Salves and ointments — Face powders — After bathing — Wool — Rabbit hair — Silk, rayon — Winter underwear, etc.)

Any other symptoms. (State causes—use other side of sheet for this and for above answers if necessary. The more details you give the more it will help to find all the causes of your trouble.)

Physical Allergy and Rheumatism Questionnaire

Your Name _____ Date _____

(In answering these questions, use back of sheet if you need more space. Use the reference numbers at beginning of questions, on back of sheet.)

1. Do you prefer hot weather or cold weather (summer or winter)?
Why?
2. How do real hot summer days affect your activities?
3. Do you perspire readily or profusely?
4. Do you take cold showers or plunges? Do you enjoy them?
Do you prefer warm or hot baths to cold tubs?
Which makes you feel better (or worse) afterwards? (Give details.)
5. Do you have or have you had rheumatism? If so, in what joints?
6. How do the following factors affect your rheumatism?
 - A. Damp weather.
 - B. Thunder storms.
 - C. Sudden temperature changes.
 - D. Cold weather
 - E. Hot weather.
 - F. Cloudy days.
 - G. Foods (name them and how they affect you).
 - H. Indigestion.
 - I. Constipation.
 - J. Infections (head colds, etc.).
 - K. Alcoholic beverages.
 - L. Sweets (candies, carbohydrates).

7. Do you enjoy physical exercise?
If you don't exercise regularly, why not?

What exercises do you take regularly?
8. Are you bothered with cold, blue hands and feet especially in cold weather?
Describe.
9. Do your hands or feet "go to sleep" frequently?
Describe circumstances under which this occurs.
Do you awaken in the night with hands tingling or "asleep"?
Give details.
10. Are you or have you been subject to fainting attacks or attacks of dizziness?
Describe.
11. Are you susceptible to head colds?
How many do you have per year?
12. What things are likely to cause colds in your particular case? (Such as drafts, chilling, movies, dust, overheating, dry air, other persons with colds, etc.)
13. If you have asthma, hay fever, sneezing attacks, hives, urticaria, migraine, sick headaches, eczema, state how any of the following conditions affect them? (Underline the preceding symptoms from which you suffer.)
- Heavy exercise
Drafts
Chilling

Getting overheated
Wind
Sunlight

Heat
Cold
Effort

Worry
Excitement
14. What other situations bring on these attacks?

Migraine Questionnaire

Name----- Address----- Occupation-----

(Use reverse of sheet if you require more space for answers.)

Which of your relatives had migraine or sick headaches? (Answer yes or no, and give number if more than one.)

Mother	-----	Mother's mother	-----	Mother's father	-----
Father	-----	Father's mother	-----	Father's mother	-----
Brothers	-----	Maternal aunts	-----	Maternal uncles	-----
Sisters	-----	Paternal aunts	-----	Paternal uncles	-----
Children	-----	Maternal cousins	-----	Paternal cousins	-----

Great-grandparents (state which and whether on mother's side or father's side).

Which of your relatives have suffered at any time from any of the following diseases?
(Designate relationship, number suffering, and disease; for example: Maternal, 2 aunts asthma, 1 uncle hay fever, grandmother eczema.)

Diseases: Asthma — Hay fever — Hives — Eczema — Epilepsy — Food idiosyncrasy.

Children -----

Husband or wife -----

Maternal -----

Paternal -----

Regarding your own attacks of headache:

Are or were your headaches right-sided-----left-sided-----both-----

Are or were they usually one sided-----or bilateral-----

Were they sometimes one sided ----- which side ----- or sometimes bilateral -----

In what part of the head do they usually localize (front, side, back, top) -----

Describe their character -----

In what manner do they vary? -----

Have you ever had any difficulty with talking during your attacks?

Describe

Have you in any of your attacks experienced numbness, tingling or pain in your fingers, hands, feet, lips, nose, or elsewhere?

Describe

Have you experienced temporary weakness or paralysis of *any* muscles during attacks?

Describe

Have you noticed or has anyone noticed that you have during your attacks, *flushing*, or *pale*ness, or *sweating* of one side of your face? (As a rule these symptoms come at the beginning of an attack, occasionally later.) Name symptoms, time and relationship to attack, whether they accompany all attacks, or only sometimes, and give whatever details you think might be of importance. State *which* side is affected.

Do the arteries in your temples get hard, cordlike, early in an attack?-----

(State which side) -----

Do you have or have you ever had any symptoms by which you can know that an attack is soon going to develop? (Constipation, indigestion, frequent urination, blurring of vision, spots before eyes, flashes of light in eyes, craving for sweets, bad breath, canker sores, hives, dizziness in eyes, etc.)-----

Describe -----

If you experience, or have ever experienced eye symptoms before or during an attack, please describe in detail (blurring, spots, flashes of light, double vision, blindness, one-sided blindness, temporary paralysis of eye muscles, etc.)-----

State which eye is more often affected; whether sometimes one and sometimes the other; usually both; always one, etc.-----

Do you suffer any mental confusion or memory impairment at onset of or during attacks?

Describe-----

As a rule, roughly, how often do or did your attacks come?-----

How long would they last?-----

Is there any *regularity* to their occurrence such as, always (or often) the same day of the week—or every ten days, or two weeks or month?-----

If there is any regularity or near-regularity, describe it in detail and give any reasons you may suspect as cause therefor-----

What percentage of them, roughly, were accompanied or followed by nausea?-----

What percentage by vomiting?-----

What percentage by diarrhea?-----

Do you or have you had attacks of indigestion (nausea, vomiting, pain, diarrhea) similar to that which you have with your headaches, but which occur *without* the headaches?-----

How often? -----

Do you think they might be due to the same cause?-----

If not, to what do you attribute them?-----

Did you suffer from repeated attacks of nausea and vomiting (often called "acidosis") in childhood?----- Describe -----

Have you had your eyes tested for glasses?----- Do glasses help your headaches?-----

Describe -----

Do your kidneys become unusually active early or late in an attack?-----

State which----- What of the following will bring on attacks?

Candy ----- Starches ----- Seafoods ----- Meats -----

What has given you greatest relief?-----

Supplementary Discussions

One would feel that with the preliminary anamnesis as comprehensive as it has been described there would be little left for the patient to tell in subsequent discussions. It is surprising to observe how much additional information the patient can often furnish after completion of the sensitization studies, after he has been apprised of the foods and other allergens to which he has reacted. The diagnostic allergic study having been completed, the examiner should review with the patient the results of the skin tests and other diagnostic measures.

Let us say that the patient has not mentioned chocolate in his previous experience nor has he indicated it as causing trouble or as suspicious in the questionnaire. He is found positive by skin test. It is surprising how often under these circumstances one will recall specific instances in which he had trouble probably due to chocolate.

The intensity of the skin reaction is not an indication. One may give a four plus reaction to a food which has never caused trouble and which on subsequent trial is found to be harmless. A borderline or plus minus reaction to

another food may be found to indicate true allergy. The patient's recollection, stimulated by the observation of the borderline reaction, may remind him of previous trouble. A frequent reaction in which this is the case is that to pyrethrum. A strongly positive pyrethrum reaction almost always indicates true sensitization. But, with a low-grade or borderline reaction, the examiner may be uncertain as to how completely the patient should avoid insect powders and sprays. Questioning usually gives the desired information. The matter of insect powders and sprays being brought to his attention, the patient will often state that he tends to sneeze or wheeze when insect sprays are used. The examiner is then in a position to rate the significance of the low-grade reaction. In this way the follow-up discussion enables the examiner to prescribe a more truly appropriate diet and the avoidance of more nearly the correct inhalant or other allergens.

In this follow-up discussion, the patient's observations should be recorded on the skin test record or elsewhere, for future reference.

Follow-up.—Even after completion of the supplementary discussion the history is not completed. The patient returns home or to his work with much new information, most of which is correct, some of which may be inaccurate, due to the limitations of the methods of study. He is now deeply interested in his problem and will be in a position more intelligently to observe his response to contact with potentially allergenic substances. He will be in a better position to do so if he has a fairly general understanding of the subject and what the physician is endeavoring to accomplish. This, he may obtain from one of the allergy manuals written primarily for the patient such as those by Feinberg (1934) and by Vaughan (1931), or, if his interest is deeper, from one of the more comprehensive monographs. Vaughan's *Primer of Allergy* (1939) has been written expressly for this purpose, and as a companion piece for the present volume.

At each return visit he may have some new, interesting bit of information from his more recent experiences. Each of these should be noted by the physician in his record of the case.

Records.—For the student of allergy, patients' records must be comprehensive. No two allergic cases are exactly alike in their symptom grouping, their sensitizations, and their response to treatment. It is only by keeping careful records that the physician can be of greatest service to his patient. These are usually persons who, due to chronicity of the disease, must remain in touch with the doctor over a period of years. It is his duty to keep a complete record in his files of all of the patient's allergic experiences during the period of observation and treatment.

It is in this way that the physician will add to our knowledge of the clinical manifestations, as they change from year to year, with new sensitizations taking the place of old, with some of the old ones persisting, with new manifestations cropping up, and possibly later with the opportunity for studying the transmission of the disease to the offspring.

CHAPTER XVIII

CONFIRMATORY STUDIES

The old adage, "all that wheezes is not asthma," is correct. A patient having presented himself for study and having given a more or less characteristic history, it is important to establish unequivocally the allergic nature of the illness. One must also recognize other nonallergic pathology.

The need for thoroughness. Pulmonary malignancy is at times accompanied by symptoms indistinguishable from true bronchial asthma. A man of middle age gave a history of having had asthma for only two months, which responded promptly to treatment with ephedrin or adrenalin. Symptoms were chiefly nocturnal. He was found strongly positive to ragweed. We thus had a patient with asthma, who gained relief with the customary treatment, and who gave positive skin reactions. However, there were no skin reactions that could be correlated with the symptomatology, since his asthma developed in mid-winter. Feeling that there was some additional unrecognized factor, we x-rayed his chest, discovering a bronchogenic sarcoma.

In this case the man had true asthma as does a person at times with a foreign body in the bronchus. In accordance with the writer's theory of the mechanism of allergy, we may say that the asthmatic response was manifested as an ineffectual effort to remove a foreign or exogenous etiologic agent.

Asthma may be mimicked by malignancy, foreign body, emphysema, bronchitis, cardiac decompensation. All hay fever or hyperesthetic rhinitis is not necessarily dependent upon an exogenous allergen. Sinus infection is a frequent factor. I have seen the extraction of an infected upper incisor tooth entirely relieve a chronic vasomotor rhinitis.

Not only do allergic gastrointestinal symptoms often resemble those of organic pathology, but conversely, organic pathology may be present with food allergy. Malignancy, ulcer, cholecystitis, appendicitis, Hodgkin's disease, etc., should be recognized when present.

Chronic or recurrent headache is not necessarily migraine nor is it necessarily due to allergy. Hypertension, threatened uremia, brain tumor, recurrent exposure to carbon monoxide, sinus infection, cervical arthritis are some examples of other possible causes.

These examples should suffice to show that one should not take it for granted that a case is primarily allergic. Confirmatory studies should be made. Even when confirmation is found, search should be made for associated non-allergic factors.

A time-saving questionnaire. To this end much more should be sought out in the patient's history. Since as much time as possible is devoted to discussion of the patient's allergic history, a simplified method for obtaining the remainder of the history is desirable. The writer has developed a questionnaire which is filled out by the patient at his leisure. The examiner later peruses the questionnaire, picking out positive replies, discussing them in greater detail with the patient when necessary.

Medical History

Name _____ Address _____ Date _____

Age _____ Referred by _____ Address _____

Note: The following questionnaire is supplementary to the history of your present illness and its purpose is to bring out any additional facts which may have a possible bearing on your illness. Your replies should be detailed enough so that they present an accurate picture of your illness. Where your answer is "yes," go into as much detail as you think necessary, using the reverse side of the sheet if necessary. Where your answer is "no," write "No." A dash or a blank space, or a check always leaves the reviewer in some doubt as to its exact significance, while "no" allows no uncertainty.

Family history:

Is your father living? -----

If so, how old is he? -----

From what chronic illness or ill- -----

nesses is he suffering? -----

If dead, from what did he die? -----

At what age? -----

Mother living? ----- Age -----

What illnesses? -----

At what age did she die? -----

Nature of last illness? -----

How many brothers have you living? -----

How many have died? -----

How many sisters living? -----

Dead? -----

Is there any tuberculosis in your -----

family? -----

How many cases? -----

Did you live with them? -----

For how long? -----

Any relatives with cancer? -----

Diabetes -----

Nephritis (Bright's Disease) -----

Rheumatism ----- Heart trouble -----

Apoplexy ----- Epilepsy (fits) -----

Nervous troubles ----- Insanity -----

Mental troubles ----- Arthritis -----

Which relatives of yours have had -----

asthma (name relationship wheth- -----

er aunts, uncles, brothers, sisters, -----

etc.)? -----

Hay fever -----

Lezema -----

Hives -----

Nettlerash -----

Eczema -----

Migraine (sick headaches) -----

What relatives have had high blood -----

pressure? -----

Low blood pressure? -----

Weight

What is the most you have ever -----

weighed? -----

When? ----- What do you weigh now? -----

Are you gaining, losing or holding -----

your weight? -----

How much? ----- Over how long a -----

period of time have you been los- -----

ing or gaining? -----

Past history:

What of the following diseases have you had: -----

(Give dates and state how long you were -----

ill.) -----

Measles -----

Mumps -----

Chickenpox -----

Whooping cough -----

Scarlet fever -----

Smallpox -----

Diphtheria -----

Influenza (grippe) -----

Tonsillitis -----

St. Vitus' dance -----

Inflammatory rheumatism -----

Pleurisy -----

Pneumonia -----

Malaria -----

Did you have chills with malaria? -----

How often did they come? -----

Typhoid fever -----

Dysentery (bloody stools) -----

Syphilis -----

Gonorrhea -----

What other diseases have you had in the -----

past? -----

What operations have you had and when? -- -----

Medical History Page 2

Name _____

Marital history:

How long have you been married? _____

Is your (husband, wife) in good health? _____

Age? _____

How many children have you living? _____

What are their ages? _____

Are they in good health? if not, state
nature of illness _____

How many children have you lost? _____

From what did they die? _____

Have there been any miscarriages? _____

How many? _____ Did they occur be-
fore the birth of other children,
afterwards or in between? _____*Cardiovascular history:*

Do you get winded easily? _____

On climbing stairs? _____

On walking uphill? _____

Are you bothered by attacks of short-
ness of breath when sitting quiet-
ly? _____Are you bothered by palpitation or
fluttering of the heart? _____Is this more pronounced when exer-
cising? _____Does it occur when you are sitting
still? _____

Will nervousness bring on palpitation? _____

Do you have any pains in or around
the heart? _____ Describe them _____

How often do they come? _____

How long do they last? _____

What makes them worse? _____

Where do they spread to? _____

What do you do to relieve them? _____

Do your feet or ankles ever swell to-
ward evening? _____

Have you ever had varicose veins? _____

Respiratory history:

Do you catch cold frequently? _____

How many colds do you have each
year? _____

Are you subject to nose bleed? _____

Do you have much catarrh in the back
of the nose? _____Do you have to clear your nose and
throat frequently? _____

Have you ever been a mouth breather? _____

Have you ever had any sinus trouble? _____

Have you ever had to have any special
examination or treatment by a
nose and throat specialist? _____

Remarks: _____

Have you ever had your sinuses
x-rayed? _____Do you suffer frequently from sore
throat? _____

Have attacks of hoarseness? _____

Lose your voice, laryngitis? _____

Have you had your tonsils removed? _____

Do you have any chronic cough? _____

Have you had in the past? _____

Have you raised sputum over any long
period of time? _____

Have you coughed up any blood? _____

Have you been bothered by pains in
the chest? _____ When? _____

What part of the chest? _____

Were they steady or intermittent? _____

Would coughing or breathing make
them worse? _____What have you found gave best relief
from pain? _____

Have you had asthma? _____

Croup? _____

Bronchitis? _____

Night sweats (wake up with a drench-
ing sweat)? _____

Hay fever? _____

Have you ever lived or worked with
any one, so far as you know, who
has had tuberculosis? _____

Have you had your chest x-rayed? _____

Medical History Page 3

Name _____

Enterologic history:

Are you bothered by fever blisters or cold sores on the lips? _____

Do you have attacks of sore mouth, canker sores, ulcers in the mouth? _____

Are you bothered by sore gums? _____

Do you have pyorrhea? _____

Have you been bothered by bleeding from the gums? _____

Are your teeth in poor condition? _____

When were you last to the dentist? _____

Have you had abscessed teeth? _____

How many? _____

Have they been removed? _____

When were your teeth last x-rayed? _____

How is your appetite? _____

Are you bothered at all by indigestion? _____

Distress after meals? _____

Nausea? _____

Does it come before or after meals? _____

How long before or after? _____

Vomiting? _____

Before or after meals? _____

How long before or after? _____

Have you ever vomited any blood? _____

Are you troubled by gas on the stomach? _____

Do you belch gas? _____

When (before or after meals) _____

How long before or after? _____

Pass gas by rectum? _____

When? _____

Are you bothered by attacks of abdominal distention? _____

Fullness after meals? _____

Heartburn? _____

Do you have any pains in the abdomen? _____

Before or after meals? _____

How long before or after? _____

How often does the pain come? _____

In what part of the abdomen is it located? _____

Where does it spread to from here? _____

Does food relieve the pain or nausea? _____

Does milk relieve? _____

Does soda relieve? _____

Do you have any symptoms when your stomach is empty? _____

Any symptoms at night? _____

What? _____

When? _____

What gives relief? _____

Are you bothered by attacks of cramps? _____

Colic? _____ Gripping pains? _____

Are you subject to diarrhea? _____

Do the bowels move daily? _____

If not, how often? _____

How often do you take laxatives? _____

What? _____

Have you ever been jaundiced (skin yellow)? _____

Eyes yellow? _____

Have you ever had hemorrhoids or piles? _____

Have you ever noted any blood in the bowel movement? _____

That the stools were pitch black or tarry? _____

White or clay colored? _____

Any mucus or stringy material in the stools? _____

When? _____

Have you been bothered by itching of _____

the rectum? _____ How much? _____

Have you ever had a rupture or hernia? _____

Have you ever had attacks of acute indigestion? _____

Describe them _____

Have you ever been "diagnosed appendicitis"? _____

Acute or chronic? _____

Have you ever had the stomach and intestines x-rayed? _____

What was found? _____

Have you swallowed the stomach tube? _____

What was found? _____

Medical History Page 4

Name _____	
<i>Neuropsychiatric history:</i>	Throbbing?----- Piercing? -----
Do you sleep well? _____	Steady? - _____
How many hours a night on the average? _____	How often does it come? -----
Are you of particularly nervous disposition or temperament? _____	What do you do to relieve it? -----
Are you unusually irritable? _____	_____
Do you worry unusually, especially over small things? _____	How long does it last? -----
Have you been bothered by dizzy spells? _____	Have you ever been paralyzed or lost the use of any of your muscles? -----
Fainting spells? _____	Have you been bothered by numbness or tingling of any part of the body? -----
Do you have headaches: if so, how often do they come? _____	Pins and needles sensation? _____
_____	When? -----
What time of day do they start? _____	Spasms or convulsions when you were a child? -----
_____	Twitching of muscles? -----
What part of the head do they start in? _____	Where? -----
Where do they spread to from there? -----	Do you have any trouble walking at night in the dark when you cannot see where you are going? -----
_____	Do you tend to stumble more than other people at night? -----
How long do they last? _____	Is your memory satisfactory? -----
What do you do to relieve them? _____	Can you smell things, detect odors, as well as other people? -----
_____	Have you noticed any abnormality with regard to your ability to taste things? -----
Are they associated with nausea or vomiting? _____	_____
With spots before the eyes? _____	Have you any weakness of any special muscles? -----
Have any of your relatives been bothered by similar types of headaches? _____	Have you ever had any difficulty swallowing? -----
Are you or have you been bothered by pain in the back, legs, arms, bones, joints, muscles? _____	<i>Orthopedic history:</i>
Where? _____	Have you been bothered by rheumatism? -----
What brings it on? _____	Where? -----
Where does it spread to? _____	Over how long a period of time did you have rheumatism? -----
What is its character, sharp or dull? _____	Have you any deformities that you know of? -----
	Have you ever had any serious injury such as broken bones? -----

Medical History Page 5

Name _____

Renal and urologic:

Do you have to get up at night to pass water? -----

How many times? -----

How long have you been doing this? -----

During the day about how many times do you urinate? -----

Have you ever had any "bladder trouble"? -----

Burning on urination? -----

Frequent urination? -----

Slowness in starting? -----

Dribbling? -----

Has there ever been a time when you could not pass urine? -----

Or when you could not hold it? -----

Have you ever been catheterized? -----

Have you ever noticed any blood in the urine? -----

Has there ever been any pus in the urine? -----

Have you ever been bothered to any appreciable extent by pain in the bladder, or kidneys or genital organs? -----

Have you ever passed any gravel or sand in the urine? -----

Have you ever had kidney colic? -----

Do your eyelids puff up night or morning? -----

How long has this been the case? -----

Otologic history:

Can you hear as well as formerly? -----

Ever been bothered by earache? -----

Ever had running or discharging ear? ----- Which ear? -----

Are you bothered by ringing of the ears? -----

How long duration? -----

What treatment? -----

Ophthalmologic history:

Do you wear glasses? -----

Constantly? -----

For near vision only? -----

When did you last have your eyes examined? -----

Do your glasses seem to fit you? -----

Can you see as well as formerly? -----

Have you been bothered at all by failing vision? -----

Have you been bothered by sore eye, inflamed eye, pink eye, conjunctivitis? -----

Do you have any pain or aching in the eye? -----

Does light bother your eyes? -----

Have you seen double for any long period of time? -----

Blurred vision? -----

Dermatologic history:

Have you had any skin eruption in the past? -----

Eczema? -----

Hives? -----

Nettlerash? -----

Poison ivy or poison oak? -----

Itching of the skin? -----

Itching around the rectum? -----

Dandruff? -----

Falling out of the hair? -----

Boils? -----

Ulcers? -----

Any other skin trouble? -----

Describe it: -----

Remarks: -----

Medical History Page 6

Name-----

Gynecologic History

How old were you when your periods began? -----

Have they always been regular? -----

If not, describe irregularity -----

How many days do they usually last? -----

Are they profuse or scanty? -----

Do you have much pain with your periods? -----

When is the pain most severe? -----

Does the blood clot? -----

Have you had any bleeding between periods? -----

Describe: -----

When was your last period? -----

Are you bothered with mental depression before or during your periods? -----

With flushing? -----

With anxiety? -----

Palpitation? -----

What other unusual symptoms accompany your periods? -----

Have you ever had any miscarriages? -----

Are you or have you been bothered with leucorrhea? -----

Have you ever noticed any lumps in the breasts? -----

Describe: -----

Any pain in the breasts? -----

When? -----

Remarks: -----

Medical History Page 7

Name _____ Address _____ Age _____

Work:

What is your present occupation? _____

What are the conditions of your work:

Monotonous _____ Daylight or artificial light _____ Good or poor light _____

Dangerous _____ Are you chiefly seated, standing or walking _____

Fatiguing _____ Hours per day at work _____ hr.; Indoors _____ hr.; Outdoors _____ hr.

Dusty _____ Time allowed for lunch _____

Smelly _____ Remarks concerning any of these answers, or concerning

Noisy _____ your work in general _____

Crowded _____

Unpleasant _____

How often have you changed your work and why? _____

Home:

What are your home conditions? _____ How is your home heated _____

Room with others _____ Is there "family friction" _____

Home noisy _____ How many hours do you sleep _____

Crowded _____ Do you sleep with windows open _____

Town or country _____ Is your sleep restful _____

Time to yourself _____ Are you disturbed by children or others _____

Daily routine:

Arise at _____ A.M. _____

Breakfast at _____ What do you eat between meals _____

Leave for work at _____

Start work at _____ Are your meals regular _____

Lunch period from _____ P.M. _____

to _____ breakfast _____ min.

Leave work at _____ luncheon _____

Dinner at _____ dinner _____

Retire at _____

Diet:

How many meals do you eat daily _____

What do you eat between meals _____

Are your meals regular _____

How long do you take to eat:

breakfast _____ min.

luncheon _____

dinner _____

Medical History Page 8

Name _____

Diet: How many times per day or week (specify which) do you eat the following:

Meat----- per-----, fish----- per-----, eggs---- per-----, green vegetables (spinach, cabbage, lettuce, turnip greens, etc.)----- per-----, potatoes (or rice, macaroni or cereal)----- per-----, pie, cake or pastry----- per-----, fruit----- per-----, salads----- per-----, candy----- per-----.

How many slices of bread, or biscuits do you eat per meal?----- Do you add much salt to your food?-----

Do you like your food highly seasoned?----- How many pads of butter per day?-----

Fried or greasy foods?----- How many glasses of water do you drink with each meal?----- How many between meals?----- Glasses of milk per day?-----

Cups of tea per day?----- Coffee----- Soft drinks----- Alcoholic drinks-----

Remarks: -----

Habits: How much tobacco do you use daily: Cigarettes----- cigars----- pipe----- chewing-----? Do you chew gum frequently?----- What regular exercise do you take in addition to your work?-----

----- How frequently?-----

How much time do you devote per day or week to such exercise?-----

Remarks: -----

Do you have a movement of the bowels daily without the use of drugs? -----

If not, how often do you use laxatives?----- What?-----

What patent medicines or other drugs do you use from time to time? -----

Recreation: To what extent do you share in social, church, political, club or trade associations: -----

What are your pleasures, recreations or interests?-----

Have you a hobby? -----

How much vacation do you take per year? -----

Are you subject to worries or moods, or periods of gloom and cheerfulness? -----

Immunity: Have you been protected by vaccination against the following diseases? (give dates): Smallpox----- Typhoid----- Diphtheria--

A physical examination, as complete as in any other diagnostic study, should be made on each allergic subject with the possible exception of uncomplicated pollinosis. Even here physical examination is desirable and should at least include the head and thorax, with x-rays of chest and sinuses when indicated.

Routine laboratory studies, hemocytologic examination, urinalysis, blood Wassermann, temperature, pulse and respiration should always be recorded.

The practice of allergy cannot be successfully divorced from that of internal medicine. One is not treating a case of asthma, but a patient with asthma, and one must know all that can be learned of this patient.

Confirmatory findings.—There are objective confirmatory findings concerning the allergic state.

The patient with nasal allergy usually presents a typical allergic nasal mucosa, pale, pearly, rather boggy, and not infrequently with easily recognized mucous polyps of varying size. The rhinoscopic picture is quite different from that of nonallergic nasal or sinus infection, when the mucosa is usually reddened rather than pale. The finding of eosinophiles in the nasal secretion further confirms the diagnosis. In the absence of an acute reaction eosinophiles may be absent in the allergic nasal secretion, but if samples are obtained repeatedly they can usually be demonstrated at some time.

When sputum is available it should be examined. The examination need not be extended to demonstration of Charcot-Leyden crystals or Curschmann's spirals, but a Wright stain should certainly be made in search for eosinophiles. A Gram stain should be made so that the examiner may know the general nature of the infecting bacteria and whether or not molds are present. Search should be made routinely for tubercle bacilli.

Blood eosinophilia is confirmatory, although so variable that it is not a requisite finding.

Diagnostic program.—The writer has found it advantageous to outline in a Provisional Program, the confirmatory and diagnostic studies to be made in each case. In this way important or desirable studies are not overlooked. The following Provisional Program adequately suits our needs. Others would modify it in accordance with their requirements.

Provisional Program							
Name_____				Date_____			
Chk	Procedure	Done	By	Chk	Procedure	Done	By
----	Anamnesis	----	----	----	Phenolsulphonephthalein	----	----
----	Status praesens	----	----	----	Urea concentration	----	----
----	Questionnaire Male	----	----	----	Mosenthal (2 hourly)	----	----
----	Questionnaire Female	----	----	----	24 hour urine	----	----
----	Questionnaire Allergy	----	----	----	Night collection	----	----
----	Questionnaire Headache	----	----	----	Blood sugar	----	----
----	----	----	----	----	Blood N. P. N.	----	----
----	Check list of foods	----	----	----	Blood -----	----	----
----	Temp., Pulse, B.P.	----	----	----	Sedimentation rate	----	----
----	Graphic B.P.	----	----	----	Malaria studies	----	----
----	Wassermann	----	----	----	Erythrocyte diameters	----	----
----	Hemocytologic	----	----	----	Bleeding time	----	----
----	Kline, Kahn	----	----	----	Clotting time	----	----
----	Routine urinalysis	----	----	----	Clot retraction	----	----
----	Urine for -----	----	----	----	Platelet count	----	----

Provisional Program—(Continued)

Name _____				Date _____			
<i>Chk</i>	<i>Procedure</i>	<i>Done</i>	<i>By</i>	<i>Chk</i>	<i>Procedure</i>	<i>Done</i>	<i>By</i>
	Icterus Index				Orris, ursal, pyrethrum		
	Van den Bergh				Feather		
	Bromsulphthalein						
	Galaetose				Passive transfer		
	Liver				Autogenous dusts		
	Sugar tolerance				Autogenous molds		
	Gastric analysis				Ophthalmology		
	Biliary drainage				Powder puff (nasal contact)		
	Intestinal parasites				Nasal smear		
	Amebae				Sputum T.B., Gram, Wright		
	Ameba complement fixation				Sputum Cult. Baet. Molds		
	Vaginal smear				Pathogen		
	Residual urine				Pure cult. vaccines		
	Occult blood						
	Feces				Anaerobic		
	Stool cultures				Vincent's gums		
	Proctoscopic				Vital capacity		
	Prostatic massage				Electrocardiogram		
	Pelvic				X-ray teeth		
	Cutaneous ingestants and in-				X-ray sinuses, chest		
	halants				X-ray		
	Endermal inhalants				Basal metabolism		
	Endermal ingestants				Lumbar puncture		
	Seafoods				Visual fields		
	Trees				Leucopenic indices		
	Weeds and grasses				Milk — egg — wheat		
	Oidiomycin and trichophytin						
	Stock molds, yeasts				Physical allergy		
	Intracutaneous bacteria				Food diary A-B		
	Special				Vitamin studies		
	Prothrombin time				Nails for sulphur		
					Photograph		
	Patch, cloths, soaps						

CHAPTER XIX

SKIN TESTING

Blackley first performed skin tests as a method of identifying substances causing allergic symptoms. Schloss, Smith, Cooke, Goodale and Walker popularized the method as an allergic diagnostic procedure. The skin test would appear *prima facie* a simple procedure that any one could do correctly with no instruction or after reading the paragraph or two which usually accompany commercial test materials. It is by no means this simple. I have seen much skin testing by methods which failed to bring out the desired information. Nearly every allergist has developed his own technic, which differs more or less among them all. Criteria for the reading or interpretation of the reactions differ still more widely. I observed reactions in one nationally known allergy clinic, finding to my surprise that reactions which I would have termed one plus or two plus were being designated four plus; those that I would have designated plus minus or borderline were one plus and two plus. This illustrates the desirability of a standard method of recording. However, up to the present time no satisfactory standard has been evolved. This has been due in part to the fact that allergen extracts are made by a variety of methods and the allergist interprets reactions in terms of his own experience with allergen extracts prepared in certain ways.

What appears in this chapter is, therefore, not necessarily applicable in all allergy clinics but deals with those methods which we have developed and found efficacious.

Dermal vs. endermal.—There are two general test methods, the scratch or dermal and the intracutaneous or endermal. For several years there was considerable disagreement as to the relative advantages of the two, some claiming that only the intracutaneous test was of value, others preferring the scratch. Today the fields of usefulness of each are recognized. The scratch test is simpler and safer. The intracutaneous test is more sensitive and more dangerous when not properly used. Fatalities have been reported following endermal tests. So far as I have been able to determine from a study of the literature there have been two fatalities reported from scratch tests, one after testing with buckwheat and another with egg. There have been more from endermal testing.

We have found a combination of the two methods more desirable. The scratch test is first applied. Studies are then repeated endermally. In this way the safety factor of the former and the greater sensitiveness of the latter are both utilized. Taking foods as an example, scratch tests are applied with those foods which are judged necessary. A positive dermal reaction gives the needed information and there is no necessity for subsequent endermal testing with that particular food. Some of the scratch tests which have been negative or borderline might show positive by the more sensitive endermal technic. We, therefore, remove from the endermal test set those foods which have been definitely positive by scratch, and repeat the tests with those which have been borderline or negative. I have never seen an endermal test applied in this way, after preliminary survey by the scratch method, which has produced a dangerously severe reaction.

Those who in the early days favored the endermal technic, expressed their belief that the scratch method was too crude, gave false negative reactions too

frequently. The advocates of the scratch technic replied, calling attention to the dangers of the other method. We are indebted especially to Fineman for reconciling the two methods. Using known dilutions of test substances, he found that on an average the intracutaneous test is one hundred times more sensitive or reactive than the scratch. If the same concentration or dilution of the allergen extract were used, the endermal would have a tremendous advantage over the scratch since it is one hundred times stronger. However, in view of the early experiences with severe reactions, users of the endermal technic diluted their test material sufficiently to safeguard against untoward reactions.

Different manufacturers prepare their extracts in different ways, there being no generally accepted standard. But for commercial preparation, pharmaceutical supply houses have found it most important to prepare endermal extracts sufficiently diluted to safeguard any physician, whether adequately trained in allergy or not. As a consequence, scratch test extracts are made up, let us say, in a dilution of 1/50. Endermal extracts are made up roughly in a dilution of 1/5000. This is one hundred times more dilute than the scratch. This one hundred times dilution balances the one hundred times greater reactivity or sensitivity. If the extracts are used in these two dilutions, neither has an advantage over the other. This is roughly the situation with many commercial extracts.



Fig. 25.—Very strong scratch reactions on the arm. A total of nine very strong reactions to one-fiftieth pollen extracts occurred simultaneously on this patient's arm. The possibility of such occurrence illustrates the desirability of performing this type of test on an extremity. In the event of constitutional reaction a tourniquet may be applied above the site of local reaction. This could not be done on the back.

If one would utilize the recognized advantage of greater sensitivity in the endermal reaction, one should have an extract that is proportionately stronger than the scratch.

Value of combined use.—The problem may be solved as follows: As a rule we make up scratch material in a 1/50 dilution of the dried original bulk. Whatever the scratch concentration may be, this is diluted ten times for intracutaneous testing. If the latter is one hundred times more sensitive (given the same dilution) and is diluted ten times, it is still ten times more reactive. This we have found to be a safe dilution. In this way, one may utilize the greater sensitiveness, while protecting against untoward reactions by preliminary scratch tests. With certain allergens which are likely to give very strong intracutaneous reactions, one may dilute twenty times instead of ten. Here we still have an average five times greater sensitiveness. This applies to substances such as cottonseed, flaxseed, horse dander and pollen extracts.

With some test substances it is not necessary to do preliminary scratch. This applies to bacteria, yeast and molds. Others customarily give so pronounced scratch reactions when positive, that endermal testing is rarely necessary. This applies especially to pollen extracts. With foods and other inhalants the two series of tests are done.



Fig. 26.—The Savonarola chair, designed by a Florentine monk, which has no back and is especially appropriate for skin testing on the back.

Scratch test technic.—The writer once saw an asthmatic who had been tested with forty extracts in an area measuring one inch by three inches. The scratches were small and necessarily very close together. The examiner had reported that all reactions were negative. On the same day we repeated the tests with all scratches at least an inch apart. Several positive reactions were observed. Wherever possible, tests should be applied an inch or more apart. Reactions may be read with greater ease. There is less danger of a positive reaction spreading to adjoining test sites. A positive reaction too close to a nearby scratch or endermal test will influence the latter, tending to make it positive even though actually it is negative. This results in a false positive reaction. Even when tests are an inch apart, one occasionally sees a strongly positive reaction an inch or more in diameter which will influence neighboring test sites. Usually, one inch separation is sufficient. When a reaction does appear so strong as to influence the neighboring sites, one should repeat the latter elsewhere, thus determining whether the reactions are true or false positives. One might routinely separate the tests by two inches, but since this occurs only occasionally, one inch is a safe distance, provided the examiner realizes and controls the possibilities for error.

Size of scratch. The preferred length of scratch varies in different clinics. They should be uniform in each case studied since the interpretation depends in part upon comparison of all reactions on one particular type of reactive skin. Some with dermographic tendency will show slight whealing or erythema at every test site. Others will show none except with positive reactions. A negative reaction on the first type of skin might be designated two or three plus on the second. Therefore, the significance of a reaction depends upon the general character of all reactions in the particular case.

The shorter the scratch, the less will be the probability of sufficient allergen extract coming in contact with tissue cells. The test should not be too short. The longer the scratch the greater will be the nonspecific traumatic reaction. A scratch of approximately three-sixteenths inch serves very well.



Fig. 27.—Testing table used by the author, designed on the principle of the Savonarola chair, with broad arm rests, thus facilitating skin testing either on the arm or back and with wing extensions for testing materials, patient's record, etc. The height of the seat (32 inches) is that of a regular examining table, a convenient working height if the technician is standing. Foot rest makes the patient more comfortable.

Character of the scratch.—The knife or needle should not be too sharp. The scratch should be more of a microscopic tear than a cut. The aim is to expose as many tissue cells to the extract as possible. A clean cut does not accomplish this as well as a slightly ragged one. Sharp cuts are more likely to draw blood. This should be avoided. For this reason we have discarded razor-sharp blades such as Bard-Parker. For a time we used the chalazion knife, recommended by Piness. This works satisfactorily and is of proper sharpness. We have since found that an ordinary needle accomplishes the purpose better and is less painful. An ordinary biologic teasing needle with bone handle serves adequately. Sewing needles may be used. Needles should be sterilized for each patient and may be kept sterile in quantity.

The direction of the scratches is of little importance. As a rule, they are applied transversely. We prefer vertical scratches on both the arm and the

back. The skin must be tensed by the thumb of the left hand as the needle is drawn in the opposite direction. When scratches are placed horizontally in a vertical line, the left thumb must be moved for each scratch. With vertical scratches the left thumb need not be moved.

Location on the body.—Alexander and McConnell have studied the reactivity of the skin of various areas. The skin of the back and abdomen is



Fig. 28.—Materials for scratch testing. The ordinary biologic teasing needle is preferred by the writer. Fresh sterile needles may be used for each patient. The needle is sharp enough but will not cut so deeply as to draw blood. The chalazion knife, first recommended by Piness, serves adequately. Only the point is used. This is not kept so sharp that it will cut deeply and draw blood. Test material may be kept in a small bottle and removed with a platinum loop imbedded in the cork. This is transferred direct to the scratch site, after which the loop is passed through a flame and returned to the bottle. Wooden toothpicks do equally well. These are discarded after each application.



Fig. 29.—Method of using chalazion knife. The point of the knife is used, not the sharpened cutting surface across the end. Three point tension on the skin, with traction away from the fingers, facilitates a clean cut.

more reactive to allergens and histamin than other parts of the integument. Next, in order of sensitiveness, they found the flexor surface of the arm, that of the forearm and the inner aspect of the thigh.

For more delicate reactions the back is to be preferred. The writer customarily performs scratch and endermal food tests on the back (positively reacting scratch foods having been previously removed from the endermal board); also the scratches with inhalants other than pollens.

On the other hand, some test materials are likely to be highly reactive when positive. These are better done on the flexor surface of the arm and forearm. This applies especially to pollens and endermal inhalants. The advantage of the arm lies not only in its slightly lessened reactivity but also in the fact if a very pronounced reaction occurs, sufficient to cause systemic symptoms, a tourniquet may be placed on the arm above the site of the reaction, thereby preventing absorption into the systemic circulation.

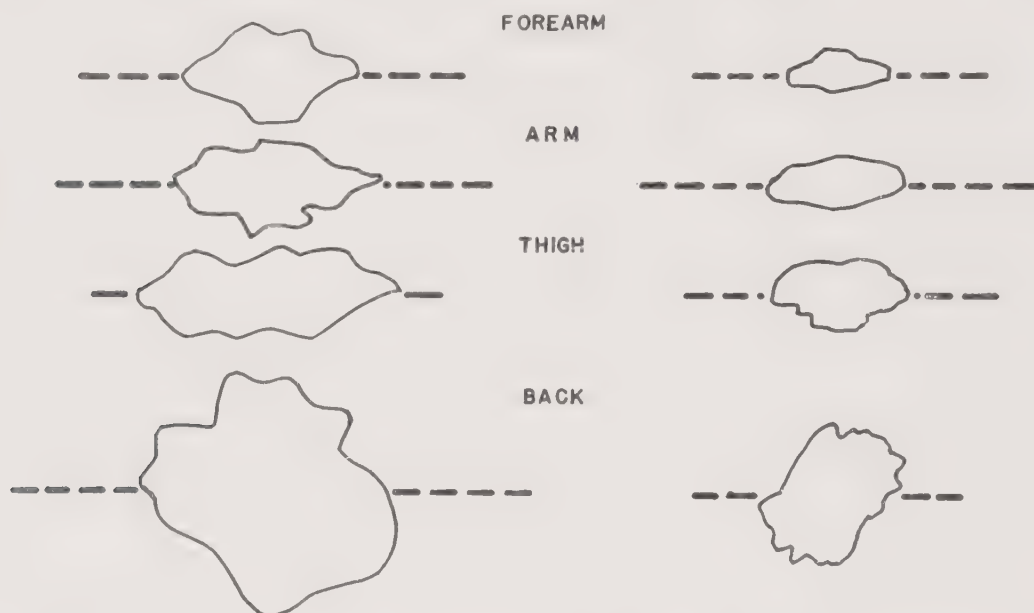


Fig. 30.—Variations in the size of the skin reaction when applied to different parts of the body. Record of comparative sizes of duplicate scratch tests to one-fiftieth ragweed extract applied to different areas, made by the writer in 1927. This previously unpublished chart confirms the more quantitative endermal series reported by Alexander and McConnell (1930). The back and abdomen appear most responsive, the arms, thigh and forearm less so.

The thigh is rarely used, because injections are somewhat more painful, and because the skin is not quite as reactive. Occasionally, the abdomen must be used, particularly in cases of dermatitis where other available or desirable areas are involved.

In general the effort should be to do skin tests on normal skin. Allergically reacting skin (dermatitis, urticaria) should be avoided. Healed scar tissue may react as well as normal skin. A man had been extensively burned, about half of his back being chiefly scar tissue. Scratch and endermal testing in normal skin areas and in the scar tissue showed similar types of reactions.

Single puncture method. The puncture method has been recommended for dermal testing (Freeman, 1930). A drop of test solution is placed on the skin. The needle point is passed through it, and, at rather a sharp angle, into the epidermis. The needle may be solid or hollow. Positive reactions may be as pronounced as those following scratch. This is not recommended, since it is as painful as the scratch and because reactions which are very low grade

to scratch may be negative following needle puncture. Hollow needles should not be used. The difficulty of completely removing the test extract is obvious.

Application of test substance.—Scratch test materials are customarily available either as dry powder or in solution. When the dry powder is used the following procedure is recommended:

1. Make the necessary number of vertical scratches described above, using an ordinary needle (sterile) in a suitable holder or a hypodermic needle attached to a syringe as holder.

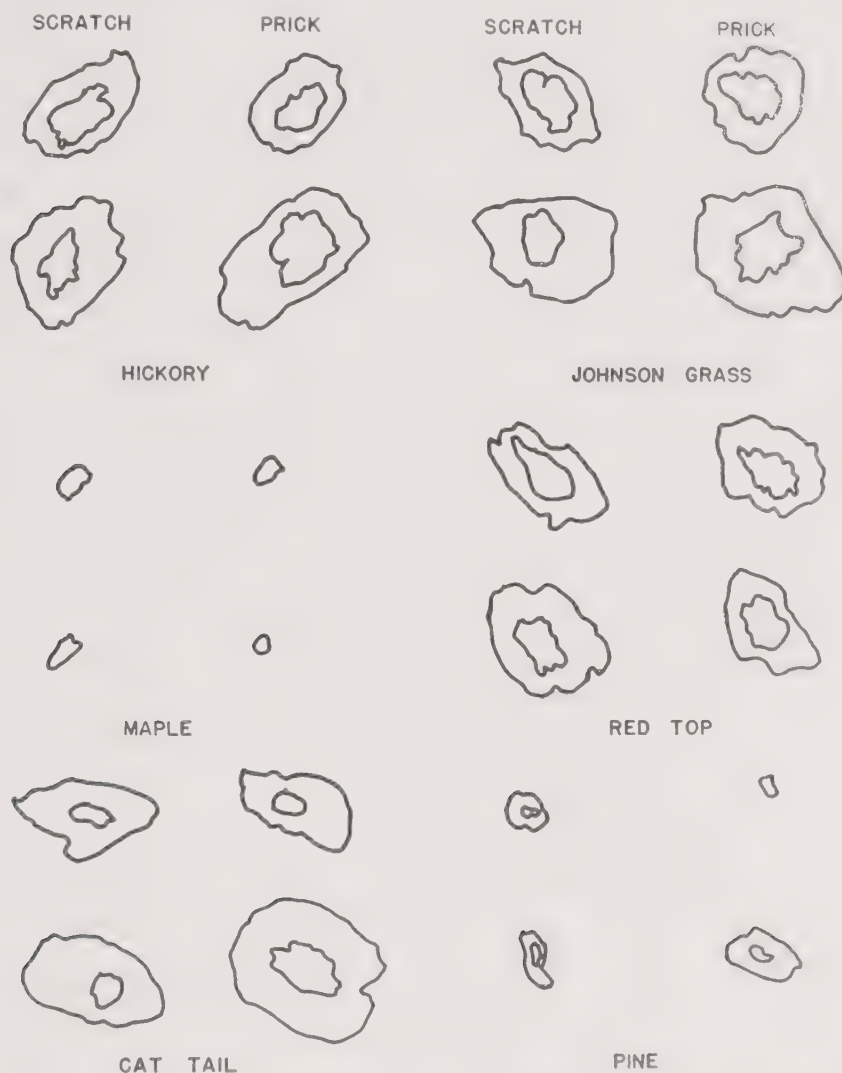


Fig. 31. Comparative reactions to scratch and single puncture or prick tests. A single prick with, in this instance, a hollow hypodermic needle, gives as strongly positive reaction as does a one-eighth inch scratch.

2. Apply a drop of suitable fluid to each scratch. Solutions commonly used are N/10 NaOH, N/100 NaOH, and physiologic saline.

3. Dip a flat-end toothpick into the powder, lifting out as much as will be held on the terminal one-eighth inch of the pick. Apply this to the drop covering the scratch and rub it in thoroughly, making a paste. Bear in mind that the only area in which this will be active is along the scratch. Too wide a spread is wasteful.

4. Keep the paste slightly moist with additions of the diluent if necessary, using a toothpick for this purpose, until time to read the reaction.

5. Use a fresh toothpick for each test.
6. Apply a control test with the extracting fluid only.

When the scratch test extract is available in liquid form, the following procedure is recommended:

1. Make the scratch as above.
2. Dip toothpick into the extract solution, transferring a small drop directly to the scratch.



Fig. 32.—Both wheals and flares show equally well following scratch or prick testing. To avoid contamination from one solution to another a nonhollow needle should be used. Patients usually find this as painful as the scratch test. Scratch reactions, left; prick reactions, right.

3. Replenish if necessary until time to read the reaction.
4. Use fresh picks each time.
5. Apply control test.

The following is satisfactory if one prefers to use commercial extracts in powder form while taking advantage of the ease of application of a solution. Most commercial dry powders are furnished in 25 or 50 mg. vials.

1. Procure 3 or 5 cc. rubber stoppered vaccine vials.
2. Pour 50 mg. of dry powder into the vial. Add 2 cc. of "glycerosaline solution" (NaCl 4 gm., glycerin 46 gm., distilled water 50 gm.).

3. Mix thoroughly. Not all of the powder will dissolve but the suspension need not be filtered. The material transferred to the skin scratch will be both in solution and suspension.

4. Transfer may be accomplished with toothpicks as described above. Another method is the use of solid stoppers into the smaller end of which a twenty gauge rust-proof wire has been inserted, the free end bent to form a loop. When the vial is stoppered the loop dips into the extract. All that is necessary is to remove the stopper, touch the loop to the scratch, pass the loop quickly through an alcohol flame, and reinsert the stopper into the vial.

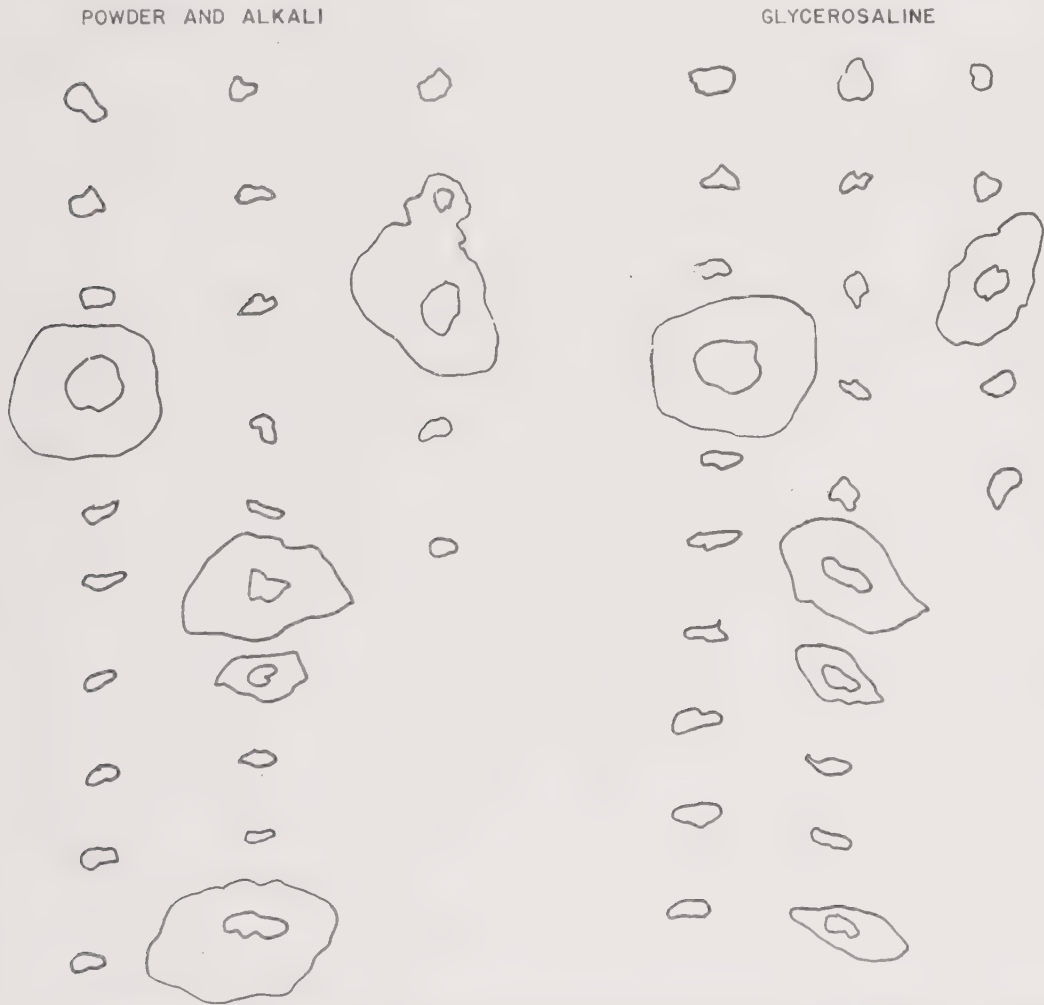


Fig. 33.—Comparison of glycerosaline and dry powder scratch tests. Duplicate determinations using (left) dry powder test materials moistened with a tenth normal sodium hydroxide and (right) glycerosaline extract of same. True positive reactions are the same in both series. Negative reactions, such as the last six in column 1, are more clearly negative with powder and alkali. Glycerosaline appears to be slightly irritating and one's standard of negativity must be adjusted thereto.

The loop should not be heated red hot. A single quick passage through the flame should be sufficient to destroy spirochetes or other organisms. The wire should be cool enough so that it may be held against the back of the hand or the cheek before reinsertion into the extract. Passage through a stream of running water prior to flaming is desirable. Dipping into a dish of water is not desirable since this introduces the possibility of mixing of allergens in high dilution.

Another method is to use capillary tubing and small bulbs as stoppers for the bottles. A small amount of extract is drawn into the capillary tube and streaked along the scratch. When glycerin-saline extracts are used the capillary tube may be replaced in the bottle without sterilization. The glycerin present seems sufficient to protect against contamination.



Fig. 34.—Comparison of dry powder moistened with alkali, with glycerosaline scratch tests. Some reactions are more strongly so with the former, others with the latter. Duplicate scratch determinations with dry powder and alkali or with glycerosaline extract would probably show as much variation. In this case the nonspecific irritation due to glycerosaline is not as apparent as in the preceding figure. Individual skins respond somewhat differently.

Diluent.—Any suitable solvent may be used such as physiologic saline, N 10 NaOH, N 100 NaOH, buffered saline (Evans), alkaline extracting fluid (Coca), or glycerosaline. The advantage of the last lies in its preservative qualities. It has a slight disadvantage, not sufficient to outweigh the advantage, in the fact that glycerin is slightly irritating and the negative reaction is not quite as clearly negative as with dry powder and tenth normal hydroxide. One's criterion of negativity is, therefore, slightly different. The frankly negative glycerosaline reaction might be called borderline as compared with the frankly negative dry powder and alkali.

Reading and interpretation of reactions. Reactions are customarily read at the end of thirty minutes. Occasionally they are at their height sooner. Less frequently they show up after a longer period, even as long as an hour, still manifesting the characteristics of an immediate or early reaction, with a small urticarial wheal with or without pseudopodia and a surrounding zone of erythema or flare. At the end of thirty minutes the test substance may be wiped off with damp cotton. If this process causes traumatic erythema, as occasionally occurs when the dried powder adheres to the skin, a few minutes should elapse before reading, until this nonspecific reaction has subsided.

If several patients are being studied at the same time or if, for any other reason, the examiner might be forced to vary the time intervals for reading, he can quickly designate the intensity of the reaction on the patient's skin, using a black eyebrow pencil. This has an added advantage that any pronounced reaction at fifteen or twenty minutes which might be fading after thirty minutes may be temporarily recorded. A black dot next to a scratch indicates a borderline reaction at the time the observation is made. A small arc of a circle indicates low-grade positive. A semicircle would indicate strongly positive, while a complete circle would be the record of a strong reaction.

This graphic temporary record has further advantages. Assuming that a large number of scratch tests, 60 or 100, are being applied to the back, the mere application requires a not inconsiderable period. Reactions are to be read at thirty minutes. Thirty minutes after the last scratch is more than thirty minutes after the first. Yet, one would wish to make the final record at one time. With the flesh pencil one can make temporary records on the skin at the proper interval for the early scratches. At the final reading, the early tests, let us say the first half, are already fading, and therefore not directly comparable to the reactions observed in the second half. The flesh pencil has recorded the earlier peak reactions. Final notations are made in the patient's record simultaneously for both early and late readings.

If technicians are applying the tests with several patients under observation, the physician can make rounds every fifteen minutes, recording the status of the reactions each time. He may then dictate his final readings even later than after thirty minutes.

Criteria.—What type of reaction should be designated negative? What criteria should one employ to determine whether a reaction is two plus, three plus or four plus? There is no uniformity among allergists. As a consequence, it is difficult to compare reports of different observers. Berkoff has suggested the use of a standard scale.

This is a plastocel or celluloid sheet 9 by 16 cm. ruled off in square centimeters. Holes are made with varying diameters, as follows: 0.5 cm., 1 cm., 1.5 cm., 2 cm., 3 cm. The original injection is made to cover an area of one-half centimeter. At the time of reading the reaction the scale is placed over the reacting wheal. If the 1 cm. hole covers it satisfactorily the reaction is called 1 plus. The recording is made in scales of plus, the highest or 3 cm. area being 4 plus. Intermediate size holes may be cut for further gradations.*

Some observers draw pictures of the reactions, actual size, for permanent record. This is ideal but time-consuming and scarcely necessary for routine work. Most observers prefer the plus system. This is satisfactory except that, as stated, there is no uniform interpretation.

*This "cutometer" is prepared with ease or may be obtained from G. Tiemann & Co., 107 E. 28th St., New York, N. Y.

One may establish a standard for negative, by applying a drop of the extracting fluid, containing no allergen, to a scratch. When several tests are done a number will be negative, serving as controls. One cannot choose an arbitrary reaction size as negative, since skins react differently. At one extreme is the highly dermatographic skin which will give what would otherwise appear to be very strongly positive reactions to every test including the control. We find all variations down to the entire absence of edema and erythema except in positive reactions. A nonspecific dermatographic reaction might be rated four plus if it occurred in the same size in the latter type of skin. The celluloid scale such as described above is, therefore, unsatisfactory unless provision is made for also recording the average size of negative reactions.

Standards.—We have found the following criteria satisfactory:

1. Determine the standard of negative by the general average of obviously nonreacting scratches in the case under consideration.
2. In the absence of frank dermatographism, a reaction with local edema covering twice the surface area of the negative is one plus.
3. A similar reaction or larger with pale center indicating beginning wheal formation but without definite pseudopods is two plus.
4. Reactions with pseudopods are three plus or stronger depending upon size and extent.
5. Reactions are often neither frankly negative nor yet twice the size of the average negative. These are recorded as plus minus or borderline.
6. Although it may seem like splitting hairs, it is a fact that there are reactions between the negative and borderline, just different enough from negative to deserve notation. These are recorded as plus minus minus or barely suggestive. Usually they turn out to be of no significance, but do indicate an allergenic substance just often enough to justify their being recorded.
7. The extent of the flare or surrounding erythema varies. As a rule, it parallels the intensity of the edema reaction, but not invariably. When it does do so it does not modify the above criteria. Occasionally, however, one observes what would be a one plus reaction, but with an unusual degree of flare. This will place it in the two plus category. More often a flare will raise a plus minus to one plus. Flares may also be observed in the average negative reaction and must, therefore, be interpreted accordingly.
8. Even though there are usually enough negative reactions to serve as controls, it is well always to apply a separate control, using the extracting fluid only. This, if there are several "negatives" and a few "plus minuses" among the tests, and if, in addition, the special control is plus minus (more reactive than some of the actual tests), then the first plus minuses mentioned have only a "negative" significance.

The delayed positive reaction. Not infrequently one will observe that although the scratch reaction wheal disappears more or less rapidly, the flare persists, while a small red indurated area takes the place of the wheal. This looks as though it might be a minute cellulitis or infection but after a time it also fades. This slowly developing delayed reaction may reach its height at the end of a few hours, often four to six, or may be more pronounced at the end of twenty-four. It has rather the appearance of a tuberculin type reaction. At times the immediate or half-hour reaction disappears entirely, after which the delayed reaction gradually evolves. More often the immediate reaction fails to completely disappear, merging gradually into the delayed.

Attention was called to the delayed reaction in 1922-1924 by Walker, Peshkin and Rost, Sidlick and Knowles, Shannon and by Vaughan. At that time these authors tested chiefly by the scratch method. The significance of this will be brought out shortly. The writer suggested that the delayed positive reaction constituted the logical type of response in those cases in which allergenic contact was chronic or more or less constant, as with foods eaten daily. The delayed positive is a mild clinical counterpart of the well-known Arthus phenomenon, a slowly developing reaction following frequent local injections of horse serum.

A positive delayed reaction, especially to foods, may follow an entirely negative immediate reaction. More often the immediate reaction was also positive.

Eczema is a more or less chronic disturbance which, when due to food allergy, is usually associated with sensitization to foods with which the individual comes into frequent or daily contact. Assuming a similarity to the Arthus phenomenon, one would anticipate a high incidence of delayed positive reactions. In a series of eczema cases the writer observed clearly positive immediate reactions in 61 per cent. In 35 per cent there were delayed positives. In approximately half of those showing delayed positives, the immediate (half-hour) reaction was also positive. Therefore, the delayed positive was not of particular diagnostic significance. But in the other half of those showing delayed positive, approximately 17 per cent of the entire series, the delayed reaction was of diagnostic importance. In this 17 per cent the immediate reaction had been negative or borderline. The delayed reaction had been definitely positive. The conclusion was obvious that in this series of more or less chronic allergies, all cases of atopic dermatitis due to foods, the recognition of the delayed positive was of distinct diagnostic importance.

In a series of cases with migraine 10 per cent gave positive delayed reactions of diagnostic significance in that the immediate reactions had been negative. A larger number gave delayed positives where the earlier reaction had also been positive.

The positive delayed scratch reaction was so definite in the writer's hands that he was at a loss to reconcile the findings with the statements of certain investigators, notably Cooke, that the delayed reaction is of no significance. Later, when we employed the intracutaneous method as well as the scratch, the explanation became obvious. The discussion had involved two different types of testing. The intracutaneous delayed reaction is of little or no diagnostic significance, because with a number of allergens there are non-specific irritating substances which cannot be removed entirely from the test extract and are responsible for delayed irritative lesions. They are not specific.

One who limits testing to the scratch method would still do well to pay attention to the twenty-four-hour delayed response. It is by no means as important as the early reaction. Since we have broadened the scope of our test methods to include both scratch and intracutaneous testing, we now pay little attention to the delayed reaction.

The intensity of the delayed reaction is recorded in accordance with the same principles employed for the early reaction. A slightly raised erythematous area about the size of the little finger nail (8 mm. diameter) would be one plus or two plus depending upon the general character of the negative scratches. One the size of the thumb nail (15 mm.) would usually be recorded as three or four plus.

The patch-abrasion test. Tucker and Thomas suggested a combination of the patch test with the scratch test. This is of value not so much in contact dermatitis as in atopy, when the reaction is only of the delayed positive type. The material is applied as in the scratch test but is kept in place by an adhesive covering as in the patch test. This provides prolonged contact, facilitating development of delayed positive reactions. These authors report success with this method in cases where the ordinary scratch or endermal technic has failed.

Borderline reactions.—The man who insists upon a clear-cut positive reaction and fails to consider the borderline response will often miss the specific allergenic excitant. The response is not necessarily maximal. The scratch method is rather a crude procedure, but when carefully carried out is surprisingly accurate, as checked by repetitions of the test. But we cannot be certain that enough material has passed into solution or enough has actually come into contact with the tissue cells to provoke a maximal response. Perhaps there was just enough to give only a mild reaction. I have often seen the drop of extract spread over an area of half an inch or more surrounding the scratch, the manipulator evidently failing to realize that only along the line of the abrasion is one capable of eliciting any response.

We know that immediately following an acute exacerbation negative responses are often obtained to proteins which at other times give positive reactions in the same individual. I do not imagine that a patient in such a negative phase changes suddenly from being a negative reactor to a strongly positive one. There are undoubtedly gradations during which the reaction may be borderline.

Although in the endermal test we know that the material actually gets into the skin and therefore in contact with cells, the other variables mentioned above are still active. With both dermal and endermal methods we have tested persons suspected of sensitization to some particular substance, with negative reactions and, within thirty minutes have repeated the same tests on some other portion of the skin, obtaining definitely positive responses. Certain portions of the skin appear to be more reactive at a given time than others. This is comparable to the situation in urticaria where not all of the skin reacts at once, but rather in successive sections. This being true one must admit that in the presence of frank allergy to a given substance, the skin reaction may vary at a given time anywhere from negative to strongly positive.

In a series of patients with migraine 36 per cent of the proved allergenic foods gave no stronger than borderline reactions at the time of testing. This included both early and delayed reactions. Here, borderline reactions were of diagnostic importance.

One should, therefore, record plus minus or borderline reactions, for future reference. Occasionally, one will find that a borderline reactor is of significance, while the three or four plus reactor is not.

Precautions against infection. Simple cleansing of the skin, with soap and water if necessary, is sufficient. No antiseptic need be used. After twenty years the writer has yet to see an infected test site, following either scratch or intracutaneous testing.

Daylight is always the best illumination for reading skin reactions. Artificial light is quite tricky. Occasionally, one may miss surprisingly strong reactions. This may be overcome fairly satisfactorily with the use of daylight blue bulbs in a reflector, which may be moved about and from which the

light is directed tangentially toward the test site. In this way the raised surface tends to throw a shadow, giving a three dimensional picture as contrasted with the two dimensional appearance from flat illumination.

Skin pigmentation renders reading difficult and tends to diminish the intensity of the reaction. This is seen especially in the colored race. It is also observed to a less degree in persons with sunburn or a heavy coat of tan. If a person who has recently had ultraviolet light therapy or a sunburn reaction from actinic rays, fails to give good reactions, the test should be repeated at some other time when this factor does not play a part.

Endermal Testing

With the exception of bacteria, yeast and mold extracts, the safe procedure is invariably to apply scratch tests before testing endermally with the same allergens. If this precaution is followed stronger endermal concentrations may be used, thus increasing the value of the tests. If it is not, the endermal concentration must be low enough to safeguard against severe reactions.

Many authors caution against the use of glycerin-saline extracts intracutaneously. Extracts containing as much as 40 or 50 per cent glycerin certainly give too much traumatic reaction, but dilutions containing as much as 5 to 10 per cent glycerin may be used satisfactorily. There is very little difference in the negative reactions when glycerin-saline is used and when the extracting fluid is buffered saline, and the physician may easily establish a negative which may be very readily distinguished from the reactions. Sterility may be assured by subsequent passage through a Seitz or porcelain filter. The Swinny-Seitz type filter* which may be attached to a syringe serves well for sterilizing small quantities for immediate use in individual cases. With care, the extract may be delivered direct from the filter, through the needle, into the skin.

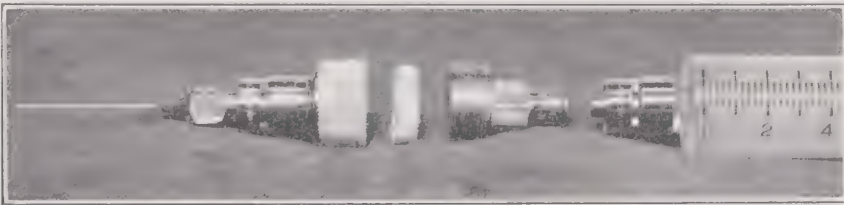


Fig. 35.—The Swinny filter containing a small Seitz type filter pad which may be attached to an all glass syringe for filtration and sterilization of small quantities of extract. (From Swinny *Journal of Laboratory and Clinical Medicine* 23: 1098, 1938. Courtesy Becton, Dickinson & Co.)

Routine.—The following instructions cover the usual endermal routine:

1. Remove from the endermal test board all allergen extracts that have already shown positive by scratch.
2. With the remainder, negative and borderline, make tests at least an inch apart, preferably more nearly two inches.
3. Use a very small gauge needle. The 26 gauge needle is satisfactory. Some investigators prefer a short bevel tip, others the usual needle point. The writer finds the usual needle point satisfactory. The needle should not be too long, one-half or five-eighths inch being a satisfactory length. A short needle usually lasts longer than a long one.
4. Use a tuberculin type syringe graduated in hundredths of a cubic centimeter. Such graduations are desirable but not essential.

*Becton Dickinson Company.

5. In filling the syringe from the rubber capped vial, be especially sure that no air remains in the hub of the needle. The syringe and needle must be entirely filled. Otherwise, one will inject air instead of fluid. Should air be injected this can be recognized at once since the character of the initial wheal differs. The phenomenon following air injection has been termed "the splash." Small air bubbles force the cells apart, giving the appearance of a very superficial wheal with minute pseudopods, a characteristic response, since pseudopods do not normally occur until at least several minutes after the injection of an allergenic extract. However, at the end of thirty minutes the splash is no longer visible or characteristic. Therefore, if a technician produces a splash the physician may make an erroneous reading after thirty minutes, unless he knows of the error.

6. Introduce the needle, bevel side up, into the superficial layers of the skin, with the barrel of the syringe almost parallel to the skin, and until the bevel is just completely buried. Then press on the plunger, introducing either 0.01 or 0.02 cc. of the extract into the epidermal layer.

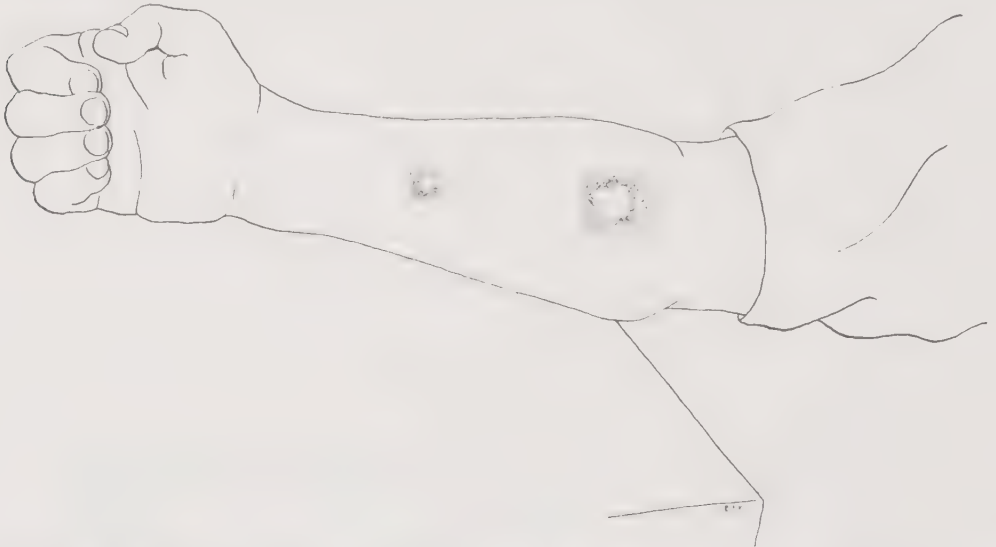


Fig. 36.—False positive reaction. This patient was tested endermally with an extract to which he was not allergic. At the left hand site 0.02 cc. was given and 0.07 cc. at the right. In order that reactions should be comparable, the same amount should be given at every test site.

For comparison of test sites, the quantity introduced must always be the same. Many persons use far too much extract. One one-hundredth cubic centimeter is ample, 0.02 cc. is more than sufficient. Some investigators use the former, others the latter, but once the amount has been decided upon it should always be the same. Lack of uniformity in the amount introduced may give the false impression of positive reactions.

Early readings are made at thirty minutes, but it should be borne in mind that with endermal tests, the most clear-cut response may be seen earlier after twenty minutes or even as early as ten minutes. At fifteen or twenty minutes clear-cut beginning pseudopodia may be observed, while at thirty these may have blended into a more general edema without pseudopods.

Interpretation. The same general principles hold for the interpretation of reactions as have been discussed with the scratch test. An early endermal response approximately twice the size of the negative, used as a control, may be recorded as one plus. If it is distinctly larger and shows definite pallor due to edema, it may be termed two plus. Any wheal with pseudopods is

recorded as two plus or more, depending upon its size. The flare may be present or absent in any response from plus minus up and, depending upon its extent, justifies the recording of the response as stronger than it would otherwise be, provided it is not a nonspecific irritative phenomenon.

With almost any set of endermal test materials, especially food allergens, certain ones may tend to produce rather more flare than others. When this is consistently the case with a given extract, one must conclude that a natural irritant in the extract has not been completely removed. After such a response has been observed on a number of cases, one adopts different standards for the negative with this particular extract. Here, therefore, the standard of negative is not only comparison with other nonreacting sites on a particular individual, but a record of the manner of response of all skins to this particular extract.



Fig. 37.—Endermal tests applied to the back. At each site 0.02 cc. is introduced. These are kept rather widely separated to avoid possible confluence of reaction.

Thus, in one batch of material we found that ginger extract always gave a strong one plus or a weak two plus reaction. For a ginger reaction to be of significance, therefore, a strong two plus or three plus reaction was required. Methods for removing nonspecific irritants are described in the section on preparation of extracts.

Another possible cause for “nonspecific” positive reactions with the endermal technic, suggested by Simon, lies in the difficulty of completely washing previous allergens out of a syringe. This suggests the advisability of always using the same syringe for the same allergen.

Type of syringe. A tuberculin type syringe graded to hundredths of a cubic centimeter is desirable. After considerable experience one can dispense with the gradations, judging the correct amount by watching the size of the primary wheal as it develops during the introduction of the extract. Ungraduated syringes are cheaper and may be used but we have preferred the greater accuracy attending the injection of a measured quantity.

The Cooke type syringe, approximately the same size and shape as the all-glass tuberculin syringe, but consisting of a glass barrel and metal plunger, the tip of which is wound with asbestos thread to prevent leakage, possesses the advantage of cheapness but the disadvantage as pointed out by Simon and Rackemann, that it is difficult to wash allergen completely out of the asbestos thread. A highly sensitized individual might give a positive reaction, not to the material used in the actual test, but to the material which has been previously used in the same syringe. Simon has recently directed attention to the difficulty of completely removing allergen extract even from all-glass syringes. Syringes should, therefore, be washed very carefully through several changes of running water. When the Cooke syringe is used, it is well always to use the same allergen in any one syringe. In this case, complete removal by washing is not as essential.

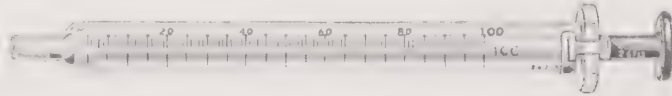


Fig. 38.—Special allergy syringe. This is the standard tuberculin syringe on which only metric system gradations appear, thus avoiding incorrect dosage from erroneous use of the minim scale. This is important (a) when the patient has occasion to receive injections from two or more physicians or nurses, and (b) when changing to an extract of higher concentration. If 9 minims has been given under the impression that it was 0.9 cc. and change is made to an extract ten times as strong, with the next dose 0.1 cc. reaction may result.

The ordinary tuberculin syringe is graduated with two scales, metric and apothecary. Patients, and doctors as well, not infrequently use the wrong scale. The writer had one experience with this which might have proved serious. A patient was receiving preseasonal pollen extract. The dose had been gradually increased until he was receiving concentrated extract. My instructions to the attending physician had been to start this concentrated extract with 0.1 cc., then 0.2 cc. and thereafter to increase the dose by 0.2 cc. each time. The patient reported in with the story that his doctor was away and wished us to give the next dose. The last had been 0.6 cc. of 1/50. We, therefore, administered 0.8 cc. In about thirty minutes the patient had a systemic reaction with generalized urticaria and asthma. Investigation showed that the physician had given minims instead of tenths of a cc. The last preceding dose had been 6 minims, not quite 0.4 cc. We had doubled this dose.

Following this experience, we enlisted the aid of Becton Dickinson & Company who now make an allergy syringe of the tuberculin type graduated only in the metric scale.

Recording of Reactions

The character of the patient's response to skin testing gives the picture of his reactive capacity at the time of the testing. Unfortunately, the picture is evanescent, disappearing quite rapidly. And yet we would like to keep this fleeting picture as a permanent record. The most accurate procedure would be by photography. Next, we might use transfer tracings outlining the actual size of the reaction. However, the purposes of the record are fulfilled by

the use of the graded plus system, provided it is used properly. In transferring the information given by the skin, to the record, one's effort should be to make the permanent record describe exactly what occurred in the skin. By this I mean especially that one should not interpret the reactions in one's mind before recording them. They should be recorded as descriptive of exactly what was observed and the interpretation should be made later, from the record. Thus, if ginger or some other food extract tends to give an irritant type of reaction, let us say two plus in all cases, and if we therefore consider this two plus reaction as negative, it should not be recorded as negative. It should be recorded as two plus with a notation to the effect that this batch of extract customarily causes a nonspecific two plus. If, on the other hand, the reaction was three plus it should be recorded as such, with similar notation, not as one plus, which would imply that the interpretation was done before the record was made. This facilitates comparison of records of skin tests made at different times.

In a dermatographic type of skin one may, therefore, see a record in which nearly all of the reactions are plus minus or one plus, in addition to whatever strongly positive reactions have been observed. When this occurs one can any time later determine from the record as well as one could have determined from the skin, the general reactive capacity or the tendency to react to simple trauma. Since this nonspecific reactivity of the skin varies in a given individual from time to time it is desirable to have the information in the permanent record.

This may be simplified somewhat, with the aims which I have just described still fulfilled, by the use of a system describing the nonspecific reactive capacity of the skin. Thus, one may record at the bottom of each skin test that the general reactivity of the skin was one plus, or quite non-reactive, using a scale up to four plus or higher, the higher grades indicating a distinct dermatographic tendency. The writer prefers a short descriptive sentence such as "skin quite nonreactive," or "rather general tendency to flares," or "skin highly reactive with distinct tendency to dermatographism," etc.

We now pay decidedly less attention than formerly to the delayed reaction. However, the twenty-four-hour reading is made and recorded. The purpose of this, particularly with endermal tests, is in great part to know what test materials contain general irritants. Thus a batch of pyrethrum extract may give a negative early reaction; three or four plus delayed. The delayed reaction is nonspecific but indicates the need for a better extract. In this case, as far as treatment is concerned, no attention is paid to the strongly positive delayed reaction. But since the record should mirror what occurred in the patient's skin, it should record the false positive, thus enabling the examiner to make his interpretation at any time subsequently.

Delayed Reactions to Bacteria and Molds

Here the delayed reaction is almost the rule. This is seen especially in reactions to parasitic yeasts and fungi such as *trichophyton* and *monilia albicans*. Such extracts may be entirely negative at thirty minutes and very strongly positive after twenty-four or forty-eight hours. The delayed reaction to these two extracts may cover an area the size of a dollar or the palm of the hand and may indeed cause regional lymphadenopathy. This is not infection even though it takes on the gross appearance of beginning cellulitis.

It gradually subsides, sometimes slowly, over a matter of several days to a week or two. This delayed tuberculin type reaction is characteristic in individuals sensitized to monilia or trichophyton who at the same time carry the organism as a skin infectant.

One also sees early reactions even with pseudopod formation. This is more likely to occur in persons with respiratory symptoms, nasal allergy or asthma. Since members of the monilia and trichophyton families are fairly common in the air, it seems probable that these are true cases of inhalant sensitization to the fungi. When the early reaction is positive, respiratory symptoms usually improve following hyposensitization.

With other air-borne fungi and with bacterial vaccines we also observe both early and delayed reactions, more frequently the latter. Both may be of etiologic significance (see section on bacterial allergy).

With the bacteria, one is likely to see both reactions, probably nonspecific in great measure, occurring quite consistently and regularly with gram negative bacteria such as *E. coli*, *B. pyocyaneus*, *H. influenzae* and *M. catarrhalis*.

There is much we do not know concerning bacterial allergy. Most of the reactions that we observe appear to be rather nonspecific, but just often enough one will achieve good results following the therapeutic use of a vaccine which has given a positive early or delayed reaction. Its use is justified especially if the patient has failed to respond to the other more clearly extrinsic allergic excitants. This is even true of the gram negative organisms mentioned above.

Choice of Test Material

Early in the investigation of allergy it was customary to list those foods which had been found to cause allergic symptoms. Today it would be simpler to list those which have not been found to do so. Even such infrequently eaten articles as cashew nuts and cranberries may cause trouble. Another difficulty in the selection of test substances lies in the fact that even though one has chronic allergic symptoms and is most likely to be sensitized to a substance with which he establishes frequent or chronic contact, he as a rule is sensitized at the same time to substances to which he is only occasionally exposed. To obtain best results one must be in a position to recognize both groups.

Since one must test not only for frequent exposure excitants, those which are more often troublesome for the major allergic, but also for many of the less frequent potential allergens, it is advantageous to have a routine test series. Obviously, this cannot include all possible allergens. There are others which will be used only occasionally, in individual cases. A routine series may be drawn up from the idiosyncrasy list, page 152.

While the employment of a testing routine with a standard minimal number of test substances, to be added to as necessary in the individual case, is a good procedure and prevents overlooking unanticipated reactions, the standard list should be selected with some intelligent discrimination. Monroe tells of seeing a 58-year-old lady being tested with mother's milk.*

It would seem unnecessary to test patients with foods which they do not eat, for it is obvious that these foods could not possibly account for the patient's allergy, and that he could not be sensitive to foods to which he has not been exposed. The possible exceptions to this statement are the infant who may have

*Monroe, Robert T., Boston, personal communication.

been sensitized in utero and the adult who may not eat a certain food but is sensitive to the entire group because he does eat other members of the group. For example, one might be sensitive to peanuts, even though he never had peanut in any form in his diet, if he should be sensitive to the entire legume group.

It is quite disconcerting to the physician when he tells the patient that he is sensitive to certain foods to receive the reply, "I never eat any of them." In spite of the interpretation of the tests as positive reactions, these cannot have any bearing on the patient's condition, and patients who are told that they are sensitive to such foods usually lose faith in the examination and the physician. Under ordinary circumstances it would seem unnecessary to test the patient with foods which he never eats, and it certainly is imperative that the physician recognize that positive skin reactions to such foods are without significance.

There should be a minimal list of routine inhalant test allergens. Persons should be tested with cat hair, dog hair, rabbit hair and similar substances even though they have no pets. They may be exposed in the homes of others and as we shall see, these substances are used in a variety of ways in nearly all homes.

The choice of pollens to be used routinely varies in different geographic locations and will, therefore, be discussed in the section dealing with pollinosis.

Questionable edema in a wheal may be established by stretching the skin over the reacting site, by pressure of the fingers on each side. This enhances the pallor. Occasionally, in mild reactions, this aids one in deciding whether there is a distinct difference between the negative and the borderline or one plus.

Subcutaneous Tests

Kahn has repeatedly expressed his belief that negative skin reactions to pollens may occur in individuals who are actually allergic thereto. He distributes such persons into three general types: (1) the extremely mildly allergic failing to give positive reactions, but reactive enough so that with high atmospheric pollen concentration, symptoms of pollinosis appear; (2) the severe pollen asthmatic who fails to react due to continuous administration of adrenalin; and (3) a group with cutaneous anergy or nonreactiveness, usually mildly allergic. The cause for "anergy" in the last group is unknown but Kahn reports that if such patients are given the usual dose of pollen extract they often react with exaggeration of symptoms. He finds that if members of this last group are kept for several days in a pollen free room, their skins again become reactive. He therefore uses this as an adjunct in diagnosis.

He believes that members of the first group, the slightly allergic, may be recognized by the subcutaneous pollen test. If the scratch or intracutaneous test or even the conjunctival reaction fails, evidence of sensitization may be found by the administration of a small dose of pollen extract subcutaneously. Positive reaction consists in the familiar delayed subcutaneous reaction often observed during treatment—a diffuse redness of the arm with swelling, heat, tenderness and sometimes associated lymphadenopathy which commences within a few hours and may last two or three days.

Bernton has also employed the subcutaneous test for confirmatory diagnosis.

Skin Reactions in Infants

It is generally understood that infants have less highly reactive skin than older children and adults. Carey and Gay have studied the reactivity

of infantile skin by the method of passive transfer of sensitivity to ragweed, following which the sensitized areas were tested for ragweed reaction. Fifteen of 18 infants so tested reacted positively but with great variation in the size of the reaction and, in general, a decidedly less extensive reaction than is observed in adults. They find that infants' skins also react less to histamine intracutaneously than do adult skins. The average size of the wheal in infants reacting to 0.002 mg. histamine intracutaneously was 0.55 cm. diameter; that of adults 1.13. The average flare in infants measured 2.2 cm. as contrasted with 5.6 in adults.

With more concentrated extracts, reactions to atopens were observed comparable in size to those in adults tested with weaker extracts.

Reliability of Skin Test Reactions

Skin reactions to inhalant allergens, especially pollens, are much more reliable than those to foods. That is, positive reactions are more likely to be true positives, indicative of trouble, and there are fewer false negative reactions. Food reactions are an accurate gauge of present sensitization in more than one-half or two-thirds of the tests. Even so, the information gained cannot be obtained in the same length of time by any other method and this makes the procedure worth while.

There can be no doubt of the value of testing with foods even though the information is not 100 per cent accurate. Sometimes a large number of positive food reactions are observed in cases where only one or two foods actually produce trouble. At other times the positive reactions to foods are so numerous as to give the impression of nonspecific responses and yet all or practically all are found to be true positives. I saw one patient who reacted to such a large variety of foods that I felt certain that most could not be actual offenders. But when mild systemic reactions were produced by intracutaneous testing with these foods and when passive transfer studies showed all of them still to be positive, I felt that they were probably true offenders. Subsequent study over a period of several months demonstrated that the patient was actually allergic to practically all of the foods to which she had given positive reaction.

Benson reports the case of a child who reacted to three-fourths of her customary foods. When all of these were eliminated she gained 30 pounds in a few weeks even though she was living on but one-fourth of the number of foods previously eaten. He also reports a woman who had been off two-thirds of her varieties of foods and had been symptom-free, but who promptly experienced a return of symptoms when she tried to eat any of them.

The final criterion of the significance of positive tests is clinical trial of the food. Often it is found that very few are actually important and, particularly in children, it is surprising how often one single food accounts for the allergic condition.

CHAPTER XX

PASSIVE TRANSFER

Over thirty years ago Rosenau and Anderson showed that a characteristic of experimental anaphylaxis was the possible transfer of sensitization from an anaphylactic animal to a normal one. The recipient of sensitized blood became sensitized or anaphylactic and remained so for several weeks, after which this acquired or passively transferred sensitization gradually disappeared.

The fact that, as shown by Dale, Schultz and others, a certain time must elapse (usually about four hours) before the recipient would respond, with anaphylactic shock, to injection of the antigen, was one of the strongest points in the evidence substantiating the cellular rather than the humoral theory of anaphylaxis. A latent period was necessary for the hypothetical antibodies to attach themselves to tissue cells. As long as they remained in the circulation, unattached, anaphylactic shock would not occur.

Early in the study of clinical allergy the fact that animals could not be passively sensitized to allergens following the introduction of human sensitized serum was put forward as an argument against the identity of experimental anaphylaxis and clinical allergy. It will be recalled that another argument against an identity was failure to demonstrate antibodies in human allergy, failure to show the presence of precipitins in the blood.

However, as we have seen in other points of apparent difference, with a clearer understanding of both the clinical and experimental phenomena, these apparent differences have gradually become increasingly reconciled, to the point where we now realize that man differs no more from the guinea pig or other animals in the mean of his response than do the various species of animals themselves.

In 1919 Ramirez reported a case of human passive transfer entirely comparable to the experimental phenomenon. A patient with pernicious anemia received a blood transfusion from a donor who was a horse asthmatic. A few days later the recipient while riding in a horse-drawn vehicle, had an attack of asthma for the first time in his life. Doerr cites a number of examples of passive sensitization following transfusion from allergic donors. Duke records a reaction after transfusion with the blood of a patient who had taken milk a short time previously. This also occurred in a recipient allergic to tomato and cabbage, both of which had recently been eaten by the donor.

Vaughan and Pipes have recorded two similar cases. In the first the recipient was sensitized to egg. The donor ate eggs shortly before transfusion. Blood matching had been correct. After receiving 75 cc. of blood the patient experienced severe dyspnea. As an allergic individual he had suffered from eczema but had never previously had asthma. Adrenalin brought relief. The second transfusion reaction occurred in a milk sensitized individual.

Such cases of passive transfer of sensitization appear not to be frequent. However, one must realize that transfusions are not very frequent; that

donor or recipient or both must be allergic; and that the donor must be exposed to an allergen to which the recipient was sensitized, or that the recipient must subsequently be exposed to a substance against which the donor was allergic. Therefore, the infrequency of reports of passive transfer following transfusion does not necessarily indicate that it would still be infrequent if these requirements were always fulfilled. On the contrary it seems probable that whenever these requirements are fulfilled one may expect an allergic transfusion reaction.

That this is probable is further indicated by the miniature transfers of sensitization first reported by Prausnitz and Küstner in 1921.

Küstner was sensitized to fish, while Prausnitz had hay fever. A small amount of Küstner's serum was introduced into the skin of a nonallergic individual. Theoretically this small skin site was passively sensitized to fish allergen. Subsequent testing with fish extract at this same area on the nonallergic individual resulted in a typical positive reaction, indicating that the area had actually been sensitized. A control test elsewhere on nonsensitized skin was negative. Although they were unable to do likewise with Prausnitz's serum, de Besche later succeeded in doing so.

Coca, Walzer and their collaborators have made extensive studies of this phenomenon. They demonstrated that, in general, passive transfer could be accomplished only in those cases in which the allergic individual displayed positive skin tests. Where the skin reaction was negative, as in contact allergy or drug idiosyncrasy, passive transfer was not accomplished. The inference appeared obvious that some reagent body existed in the blood of persons giving positive skin reactions to the particular allergen, which did not exist in other allergies. This reagent substance could be transferred passively. For it, Coca suggested the name reagin. The fact that in contact allergy and drug idiosyncrasy reagin could not be demonstrated was one of the reasons for Coca's suggestion that in these three conditions we were dealing with different types of phenomena. To distinguish them he proposed the term atopy to designate the type of clinical allergy in which positive scratch or endermal reactions were observed and reagins could be transferred passively. Since, not infrequently, one has occasion to distinguish between these forms of allergy, the acceptance of the term atopy in the terminology of allergy appears entirely logical. When used in the present discussion it will be employed to designate a subdivision of the more general field, an artificial subdivision based upon the presence or absence of a certain phenomenon.

We are indebted especially to Matthew Walzer for the introduction of the passive transfer technic into the routine of diagnosis. In 1924 he was called upon to study a one-year-old asthmatic patient in whom skin testing was impossible on account of an associated eczema and urticaria. It occurred to him that the Prausnitz-Küstner phenomenon might be applied. He obtained the patient's serum, introduced it into a nonallergic recipient, and performed the tests on the latter. Success with this first case led him to develop a routine technic.

Since his first report (1925) the technic has come into general use. Walzer termed it "the Indirect Method of Testing." Other commonly used terms are "the Prausnitz-Küstner Reaction," "P-K reaction," and "Passive Transfer."

This is not a routine diagnostic procedure but becomes most useful under certain circumstances, as in individuals with such extensive dermatitis that skin tests cannot be done, or in infants and young children who protest too violently against testing. Walzer lists the following indications:

1. Abnormal skin conditions of the patient, including:
 - a. Acute and chronic atopic eczemas in children and adults, with or without secondary infection.
 - b. Icthyotic skins and those scarred by constant scratching and inflammation.
 - c. Urticaria.
 - d. Marked dermatographism.
 - e. The presence of a contagious skin infection, such as impetigo.
 - f. The presence of diffuse skin eruptions.
 - g. Hyperirritability of the skin in babies.
2. Constant and severe asthma necessitating almost uninterrupted use of epinephrin.
3. Cases of extreme sensitization in infants and children, where constitutional reactions might occur on direct testing.
4. Suspected allergy in infants and children too small or too ill to be subjected to a long series of tests.
5. Antipathy on the part of the patient or his relatives to direct tests.
6. The inability of the patient to visit the physician or undergo a series of tests either because of debility, inconvenience, or lack of time.
7. The desire to check the genuineness of an unusual number of positive skin reactions elicited by direct testing.

Technic

Transfer may be accomplished using either serum or plasma.

Directions.—Sterilize a centrifuge tube and a rubber vaccine vial cap to fit. If plasma is desired, several small glass beads should be placed in the centrifuge tube prior to sterilization.

Obtain 5 to 10 cc. of blood under aseptic precautions, using a dry syringe to prevent hemolysis.

Introduce this into the sterile tube, close the latter with the rubber cap, and fasten it securely with a rubber band wrapped tightly around its outer flange. This prevents the cap from being forced into the tube during centrifugation.

If plasma is desired, shake the tube containing blood and beads for several minutes, to prevent coagulation.

Plasma tubes may be centrifuged without delay. Serum tubes should be set aside in the ice box until the clot has retracted. Occasionally, agitation without removing the stopper helps to prevent the clot from adhering to the sides of the tube.

Centrifuge thoroughly.

Withdraw the supernatant serum or plasma by inserting a needle attached to a syringe, through the rubber stopper. The stopper may be removed, but aseptic technic should be strictly preserved.

The serum may now be introduced directly into the skin of the recipient as described below.

Remarks.—The usual precautions should be taken to be certain that the donor is not suffering from any infectious or contagious disease. A Wassermann or one of the reliable precipitin tests for syphilis is a prerequisite. One of the latter such as the Kline test may be performed with very little delay, using a portion of the serum obtained by the above technic.

Although 5 to 10 cc. of blood is preferable, as little as 2 cc. may suffice.

Serum or plasma may be used undiluted or diluted as much as ten times. Dilution with an equal quantity of solution is preferred. Rarely is it necessary, in order to have sufficient quantity, to dilute more than from two to four times.

If for any reason it is considered desirable, as for instance in the presence of skin infection in the donor, sterilization may be accomplished by passage through a Seitz or porcelain filter. The serum passes through more readily if somewhat diluted. The Swinny filter* attachment for syringes facilitates combined filtration and transfer in a single procedure.

The diluent should be physiologic saline.

If it is not desired to immediately transfer the serum or plasma to the skin of the recipient, it may be transferred under aseptic precautions to a sterile vaccine vial. Phenol to a final concentration of 0.4 per cent may be added or an equal volume of physiologic saline containing 0.4 per cent phenol may be added. However, as little alteration of the serum as possible is desired. Our own experience is that if one's aseptic technic is reliable, serum may be kept in a vial in the ice box without addition of preservative.

Transfer to Recipient

Whenever possible the recipient should be directed to avoid ingestion or inhalation or other contact with the substances to be tested. Otherwise atopen brought to the test site through the blood may neutralize reagin prior to the actual test, thus resulting in an apparently false negative reaction at that time.

Walzer recommends the flexor surface of the arm for skin test sites. The forearm is not as responsive. The writer prefers the back. Either appears to be satisfactory.

Using the back, areas to the left of the spinal column are passively sensitized. A checkerboard area is plotted on the left half of the back with the squares one inch on a side and beginning at some easily recognized anatomic landmark such as a mole or, in the absence of such, the vertebra prominens. The squares are not actually drawn but with a straight edge the points of intersection of the imaginary lines are indicated by dots made with the flesh pencil. The first horizontal line is usually made two inches below the vertebra prominens. The spinal column is not approached too closely, the inner column of dots customarily being about two inches from the spinal processes.

Three or more vertical columns may be placed on the left half of the back with eight or more dots to a column.

Introduce the serum intracutaneously following the technic described in endermal testing, selecting a point each time one-fourth inch to the right of a dot.

Introduce a larger amount than is done in endermal testing. In the latter 0.01 cc. or at most 0.02 cc. is used. In producing passive transfer 0.07 cc. to 0.1 cc. is introduced.

When areas corresponding to each dot on the left half of the back have all received intracutaneous injections of serum, the dots may be removed.

If the arm is used, a single row is sensitized on each arm, off center by about one inch, on the flexor surface. The rows may be annular, across the arm, or longitudinal, down its length.

*Becton Dickinson.

For control reaction sites, on the arm, another row will later be applied about one inch off center in the other direction, making the test site and the control site an inch and a half or more apart. When the back is used, the entire right side of the back is available for control tests.

Do not attempt testing until the traumatic reaction of transfer has subsided.

Remarks.—The subject for transfer should by preference be a so-called nonallergic individual, that is, he should certainly not be a major allergic. Walzer and Bowman have shown that allergies do not accept passive sensitization with the same regularity or to the same degree as do so-called non-allergies. Even among the latter Coca finds that about 50 per cent do not satisfactorily accept passive sensitization.



Fig. 39.—The effect of mechanical or chemical irritation. Sites on the left half of this subject's back had been previously sensitized. Each site was ringed with silver nitrate. Two days later when testing was attempted, every site reacted, non-specifically, with a wheal completely and accurately filling the ring made by silver nitrate. Flares extended beyond. Symmetrical control tests on the right half of the back showed no more than the usual number of positive reactions. Physical and chemical trauma should be avoided.

If only an allergic recipient is available, he may be used, but one cannot be as confident of satisfactory readings. There is this to be said, that a positive transfer reaction in an allergic person who is not sensitized to the particular allergen giving the positive reaction is no more strongly positive than in a nonallergic. Similarly there is no difference between the negatives. The chief difficulty is encountered when the allergic person is also sensitized to

the test substance. Walzer's observations, however, lead one to infer that there is more to it than this simple obvious fact. The allergic person does not respond quite as satisfactorily as the nonallergic.

The observations of Cohen and Rudolph and of Brunner and Walzer may have some bearing on this. The former found that if an allergen is applied to the nasal mucosa of an allergic, it appears in the blood (at a passive transfer site) after a longer delay than under similar circumstances in a non-allergic individual. The latter group found the same to be true when the allergen is introduced through the skin. This would indicate that in the allergic there is some factor that delays absorption or at any rate delays reaction in a sensitized site.

The sites of introduction of the serum should be carefully mapped since it is desirable to introduce the test substance at as nearly the same place as possible. If testing is done within twenty-four or even forty-eight hours the points of needling can usually be recognized. But if longer time elapses, identification of the sites becomes difficult and a reconstruction of the checker-board mat must be made. There is evidence that a passively sensitized zone of skin, perhaps one inch or more in diameter surrounds the point of inoculation. But highest sensitization will be found at the center of the zone and this is the area which should be used for best results.

Indeed, Rackemann states that not only should the needle be reintroduced when testing with the allergen, directly along the line of the previous needle puncture, but it should even be introduced in precisely the same direction. He reached this conclusion following a series of aberrant responses when one technician introduced the serum with the needle pointed toward the shoulder while the second technician who injected the allergen worked with the needle directed toward the hand. When the back is used this variation is not as likely to occur unless a technician be left handed, since the syringe is almost invariably held horizontally in the right hand with the needle pointing toward the left. Under any circumstance it is obvious that the identical site should be tested if possible.

A certain time should elapse between the procedure of serum introduction and that of testing. Coca has observed that, as with experimental passive anaphylaxis in animals, there is a negative phase of at least two hours, during which we might say that reagins are becoming fixed in the tissues. Four hours is about the earliest interval after which positive reactions may be observed and as a rule they are decidedly better at the end of twenty-four to forty-eight hours. Passive sensitization persists as a rule for about four weeks, after which it gradually declines.

There is another reason for delay. Bowman and Walzer have studied refractoriness of the sensitized area. The area may become refractory either because of an immunologic factor or because of a tissue factor. If a site is sensitized to ragweed, and subsequent testing is done with ragweed extract a positive reaction ensues. Thereafter, this particular site no longer reacts to ragweed extract. The site is refractory in an immunologic sense. Desensitization has been accomplished through union of reagin and atopen. If the same ragweed serum also contains reagins to horse dander, the identical test site will still react to horse dander extract. The refractoriness is specific.

Nonspecific tissue refractoriness is due to trauma. Using the same serum containing ragweed and horse dander reagins, let us assume that two sites have been sensitized and that one of them has already been desensitized with

ragweed extract. Shortly after the reaction has subsided both sites are now tested with horse dander extract. As stated, the first (ragweed tested) site will still react to horse dander but the reaction is not as pronounced as in the second site which has not been traumatized by the recent ragweed wheal. If, instead of testing both sites with horse dander extract shortly after subsidence of the ragweed wheal, a week or more elapses before the second testing, then both sites will react equally well to horse dander extract. The whealing capacity of a skin that has recently been traumatized is non-specifically impaired for a time. There is a temporary tissue refractoriness. Bowman and Walzer find that its duration varies but may cover four or five days, occasionally as long as three or four weeks. As a consequence Walzer emphasizes that in clinical testing a site which has once responded with whealing should not be used subsequently for other testing even though the subsequent allergen be different.

The degree of refractoriness appears to depend in a measure upon the degree of trauma. The simple trauma of needling and distention of the epithelium in the introduction of serum produces some refractoriness. A histamin wheal produces more, but not as much as the whealing caused by local allergic reaction. The possible explanation of this refractoriness in terms of H-substance exhaustion is obvious.

Sites which have been negative to passive transfer may be used again, but it should be borne in mind that even so there is a refractory phase. Ideally, from two to four days, more nearly the latter, should elapse between passive sensitization and the first testing; four days between the first allergen testing and any retesting of the same sites; and sites that have responded positively to any degree whatsoever should not be used again.

Testing With Allergen

As stated, at least four hours, preferably forty-eight to ninety-six should elapse between passive sensitization and final testing. The test extract should be introduced as nearly as possible into the identical areas, along the same needle puncture and in the same direction.

For final testing the procedure is applicable to both the dermal and endermal technics, although the former is less desirable since it produces more trauma and further increases the refractory state.

The same concentration of extract may be used that is employed in direct endermal testing. Somewhat stronger concentration is usually also safe. If the recipient is allergic he should first be tested by the scratch technic for unusual sensitization.

Procedure.—Identify the original test marks, using the checkerboard method and flesh pencil dots if necessary. Remember that the sensitized sites were one-fourth inch to the right of the dots.

As with the direct endermal technic introduce 0.01 cc., not more than 0.02 cc. of the allergen extract into the upper left-hand site.

Immediately thereafter, using the same syringe and needle which was originally filled with sufficient extract for two tests, introduce an identical amount at a symmetrical point on the right half of the back. This would be somewhere near the right shoulder.

With a fresh syringe, similarly loaded, proceed to inoculate the next site, and a symmetrical site on the right side. Successive inoculation may be made

vertically throughout the length of the column or horizontally across the lines. For purposes of recording, we find the longer lines represented by the vertical columns more satisfactory.

When testing has been completed there will be two symmetrical checkerboards, mirror imaged as far as site-content is concerned. The one at the left represents the patient, the one at the right the passive transfer recipient as a negative control.

In reading the reactions bear two points in mind. (1) Reactions are rarely as pronounced as in direct testing. Any difference between the passively sensitized site and its corresponding control is of significance. What would be considered plus minus in direct testing may be considered definitely positive, although it is, of course, recorded as plus minus. (2) The reaction evolves somewhat more slowly than in direct testing. In direct endermal testing the reaction is customarily read at the end of twenty to thirty minutes. At the end of thirty minutes in indirect testing the reaction may not yet have reached its height. Usually it has done so within forty-five minutes. It should be observed repeatedly during this interval.

The record of the reaction should have two columns, the first indicating the character of the reaction of the patient (left side) and the second that of the recipient as a control (right side). Determination of degree of positiveness is not based upon the general run of negatives at a particular sitting as in the direct method but rather upon comparison of the donor's test with the recipient's test.

To read, place the index fingers of right and left hand directly below the corresponding sites (patient and recipient) for the same extract. This prevents confusion of areas. Obviously, the recording is greatly simplified if it can be dictated. In the absence of other help the recipient is usually delighted to serve as amanuensis.

Usually there are one or more positive reactions of greater or less degree on the recipient's side as well as on the patient's. These may indicate sensitization of the recipient or may be due to chemical irritation. Sometimes the reaction on the recipient's side is even stronger than that on the patient's. Sometimes both are positive to equal degree. In neither of these cases can one draw any conclusion as to the patient's sensitization. If both are equally positive it may indicate that there is a chemical irritant or it may indicate that the recipient is also sensitized. This much can be definitely said; one cannot take the stand that if the patient were also sensitized to the same allergen, the reaction on the patient's side would be still larger. This may be true but is not always true.

Dictate the intensity of the reaction on the left, then the corresponding one on the right. Follow through until all have been recorded. Do not attempt to interpret the reactions prior to recording them. For example, if the patient's site is two plus and the recipient's one plus, do not record the former as one plus, the latter as negative. Put down the actual observations. Interpretation may then be made at any time subsequently but it is important to have it in the record that the recipient also gave a certain degree of response.

When the patient's reaction is much stronger than the recipient's this probably is of significance. When both are equally strong, the test must be repeated at another time, either at different sites, not previously used, or preferably, using another recipient.

Remarks.—Mirror image application of test substances is preferable since the writer has observed a slight variation in the intensity of skin test responses near the spine as contrasted with farther away from it. Since small variations are important in passive transfer, this is to be avoided.

Not too many sites should be tested at one time. Usually from six to eight are enough. This is because of the risk of what Walzer terms a constitutional reaction. This is altogether different from what is meant by constitutional reaction in allergic shock and, because of the possible confusion in terms, might better be called *absorption phenomenon*.

Gay and Chant observed that if a site is passively sensitized on one arm and the allergen is injected in sufficient quantity into the opposite arm the original sensitized site may react with wheal formation, even though there is no injection near the site. The allergen obviously was absorbed and carried through the blood to the sensitized area. Cohen and his collaborators confirmed these observations and further showed that the same phenomenon may occur in a sensitized skin site if the allergen is introduced by contact with the nasal mucosa. Sulzberger and Vaughan confirmed the phenomenon of absorption through the nasal mucous membrane. Walzer, Brunner and Smyth and Stallings demonstrated that allergen absorbed from the digestive tract during the normal process of digestion may likewise activate a passively sensitized skin area.

If, during the P-K test, several strongly positive reactions occur, enough allergen may be absorbed (coming both from the patient's area and the recipient's area) to produce this absorption phenomenon, with the result that all of the passively sensitized areas simultaneously become positive. These are obviously true specific wheals which will desensitize all the areas for the absorbed allergen and will also produce a long refractory phase to all allergens.

Obviously, the absorption phenomenon is to be avoided. If most tests are negative the phenomenon will not appear. Therefore, if after a reasonable time, say one hour, the initial series of six to eight tests have been completed and are not too strongly positive, one can continue with another similar series. In this way one may complete all the tests at one sitting but should proceed with due regard for the possibility of the absorption phenomenon. Flare-up at untested transfer sites during testing indicates advent of the absorption phenomenon.

The absorption phenomenon makes the recipient's diet during the period of the study, important. We have just seen that if an area is passively sensitized with a specified food reagin and the patient subsequently eats that food, a positive reaction may occur. Thereafter, the skin site is desensitized for this food. Now if, in the routine P-K, the recipient has been passively sensitized and should eat one of the foods to which the patient is allergic, all sites will become desensitized to that food and a refractory phase will ensue. Must the recipient, therefore, refrain from all foods from the time of sensitization until testing? Fortunately, the situation is not this bad. Walzer finds that certain foods produce this phenomenon much more readily than others. He has demonstrated it with eggs, fish and nuts, occasionally with banana, corn, mustard, chicken and a few other foods. He recommends that, starting with the day of sensitization, that is the day of introduction of serum, eggs, fish, nuts and any other suspected food should be avoided by the recipient until tests have ruled out the presence of allergy to these substances.

If the control reaction is stronger than the patient's reaction, the probability is that there is some degree of refractoriness in the sensitized site. In this case the test should be repeated at another site. Since areas of sunburn and tanning should be avoided, the back is sometimes a more desirable area. Doubtful reactions should be repeated on other test sites or on other recipients, or, when possible, on the patient himself.

There has been some confusion in the selection of a term to designate the nonallergic subject used for passive transfer. Some term him the *recipient*, as has been done in the present discussion, while others speak of him as the *donor*, evidently stressing the analogy to transfusion, and implying that he is a skin-donor.

Evaluation and Significance of the P-K Reaction and the Indirect Method of Testing

Several factors enter into the success of the passive transfer test. It is more reliable with pollen reagents, less so with foods. Sera with high reaginic titer to foods or pollens will give positive P-K reactions to both. Sera of low titer may fail to react, especially to foods. Not all recipients accept passive transfer. Coca and Grove (1925) found that 84 per cent of normal skins accepted transfer while 11 per cent were nonreceptive. Five per cent were slightly so. Walzer and Bowman (1931) observed that atopic individuals did not accept passive sensitization as regularly as nonatopic.

However, Rackemann and Wagner (1936) did not find a nonreceptive person among 75 allergies passively sensitized with pollen reagents. This apparent discrepancy appears to be reconciled by the work of Romanoff and Brooks (1937) who found that allergic and nonallergic recipients accepted transfer of undiluted sera equally well, but that when sensitized with serial dilutions of reaginic sera the former became nonreactive in lower dilutions. They concluded that the constancy of acceptance depends less upon the presence or absence of atopy than upon the concentration of the reagents in the serum. However, in view of their findings, it is obviously more desirable to use nonallergic recipients whenever possible.

Levine and Coca expressed the belief that the P-K reaction always parallels the direct skin test reaction. If the skin does not react, the P-K will be negative, and vice versa. In general, this is probably true but there are exceptions. Smyth and Bain reached similar conclusions but called attention to exceptions. Coca and Grove have described an interesting example of the customary parallelism. They observed two patients, both sensitized to green peas. The first, very highly allergic, would develop angioneurotic edema of the lips almost instantaneously following contact with peas, even before they were swallowed. Both direct and indirect skin testing were negative. The second patient, sensitized to the same allergen, reacted with urticaria. Both direct and indirect testing were positive, and in comparable degrees. Rackemann states that he has never observed reagents occurring without a simultaneous positive skin reaction.

Just as there may be false positive and false negative direct skin reactions, passive transfer reactions may be falsely positive or negative as far as clinical significance is concerned. Peshkin and Feinman (1929) found this the case and concluded that passive transfer is not a satisfactory substitute for direct testing. Chobot and Hurwitz (1937) found that reagents may exist which are of no etiologic significance, and that certain substances, especially foods, of proved etiologic importance may give false negative passive transfer reactions.

Tuft and Ramsdell found that twenty-one of twenty-five patients tested with horse serum were negative to passive transfer even though direct testing was positive. Coca has applied this fact in his rules for serum therapy (see Serum Disease).

Markin states that during an attack of asthma the direct skin reaction may be negative, due apparently to temporary refractoriness of the skin, but that indirect testing may be positive. Similarly, during pollen therapy the scratch reaction may become negative or nearly so, but the reagin content of the blood stays high or even increases, as demonstrated by the P-K test. This being the case, one cannot explain therapeutic desensitization following injection of allergen as due to "antibody exhaustion." There is as much or even more free circulating antibody (reagin) as before desensitization. The production of "blocking antibodies" as a result of treatment may, by uniting with the antigen, prevent the reaction within the body cells and this, rather than the circulating reagin, may protect the cells. It should be stated parenthetically that although the scratch reaction does tend to become less pronounced under hyposensitization therapy, this is not the customary observation with the endermal test.

Walzer found in a study of 200 indirect tests that 3 patients gave generalized nonspecific reactions to any and all allergen extracts. As we have seen, the absorption phenomenon (constitutional reaction) in indirect testing may produce universal positives, but these three were nonspecifically reactive, not examples of the absorption phenomenon. Walzer, therefore, advises that a saline control test always be used with indirect testing. If the saline control is also positive the reactions are nonspecific. Of course, the saline control would also be positive with the absorption phenomenon and the latter must, therefore, be ruled out.

Not all allergens, even among those which cause reagin formation, are equally effective in passive transfer. Smyth and Bain found egg allergen distinctly more effective in producing positive passive transfer than wheat, and that pollen was more effective than other inhalant allergens.

Spain and Newell have shown that the reagin content of blister fluid following the application of cantharides plaster is the same as that of blood serum. Parlato has confirmed this and suggests the possible use of this method with infants or others from whom it is impossible to obtain blood. Spain, however, advises against this except in great urgency, because the blister itself is very painful and because of the possibility of secondary infection.

Sex, age and blood group appear to play no part in the recipient's ability to accept passive transfer. Even newborn infants may be passively sensitized although their positive transfer reactions are not as pronounced as those of adults; are not accompanied by pseudopod formation. This corresponds with observations of direct testing on infants.

The Prausnitz-Küstner phenomenon has been of material aid in furthering general study of the allergic phenomena. A single allergenic substance may contain two or more specific allergens. Thus, in egg there are egg white and egg yolk. There are even fractions of egg white. A single passive transfer site may be desensitized for one allergen, still remaining reactive, after the refractory period, to others. Using this principle Bosch et al. demonstrated that the chief allergen in egg white is the albumin fraction. Walzer and Bowman studied the allergenic relationship between donkey, horse and zebra sera, showing that all contained one identical antigen and each in addition contained allergens which were not alike. Similarly, Tuft compared horse dander and horse serum, find

ing that dander may contain two organ-specific allergens, dander allergen and serum allergen, while serum contains only the latter.

Levine and Coca injected timothy pollen extract intravenously into non-allergic persons. At intervals they obtained blood from the subjects, testing it in the skin of others who had been passively sensitized to timothy. Positive P-K indicated that the serum still contained timothy allergen. The allergen persisted in the circulation for several days after intravenous injection. Cohen and his collaborators, also Feinberg and Bernstein concluded from passive transfer experiments, that pollen allergen persists in the circulation up to 48 hours. Tuft determined from precipitin tests that horse serum injected intramuscularly or subcutaneously persists in the circulation for three or four days, after which it disappears gradually, being entirely gone by the seventeenth day. Walzer and Walzer found that peanut antigen absorbed as food was still present in the blood after 48 hours.

Although reagin is not a tangible substance whose presence may be visualized like precipitin in the test tube, it is one whose presence may be demonstrated by the manner of its reaction. It is, therefore, susceptible of study. As early as 1921 Prausnitz and Küstner demonstrated that the transferred substance was neither precipitin nor complement fixing antibody. Antibodies occur in the globulin component of blood, especially the euglobulin. Smyth and Bain find reagin in the pseudoglobulin fraction. Both are globulins or occur with globulins, and both precipitin and reagin are heat resistant to about the same degree. Reagin is slightly more thermolabile, but, as pointed out by Zinsser, some antibodies are equally so.

Sherrer found reagins abundant in plasma and serum, distributed parallel with pseudoglobulin but present to a slight extent in euglobulin.

Although reagins and antibodies may not be identical their action is similar, they are distributed in the same constituents of blood, and they probably are almost identical substances, existing for an identical purpose.

Human reagins can be transferred passively to monkey skin (Walzer et al., 1938). Ramsdell has shown that reagins may be transferred from one animal to another in the same species. In this way positive skin reactions may be obtained on passive transfer. Here again we see the evidence of variation in the mode of reaction depending upon species.

Autopassive Transfer. Cowie suggests that when allergic individuals have nonreactive skins, the reactivity may be increased by introducing the patient's serum into his own skin following the usual Prausnitz-Küstner technic. He designates this procedure autopassive transfer and finds that in some instances at least reaction to specific allergen occurs as frequently and as vigorously in autopassive transfer as in heteropassive transfer.

Preservation of serum for passive transfer.—Serum may be lyophilized and kept without deterioration for at least several months.

CHAPTER XXI

MUCOUS MEMBRANE TESTS

Test substances may be applied to the mucous membranes as well as to the skin. Indeed, these were among the earliest methods used. Kirkman (1835), a sufferer from hay fever, tested himself by sniffing the pollen of sweet vernal grass. He promptly developed hay fever.

Blackley tested pollens in the same manner and by introducing small amounts on the conjunctiva. Dunbar, Noon, Freeman, Cooke and Vander Veer all used the conjunctival test in the early days of allergic study. At that time these were much more logical procedures since they represented efforts to reproduce the disease through natural channels. The surprising fact is that Blackley developed the cutaneous test, since at that time there was really no rationale for it.

Conjunctival Test

With the advent of skin testing this procedure became of secondary importance. It is used almost exclusively in testing for sensitization to pollen but may be used with other inhalant allergens. When the test was gradually falling into disuse Peshkin re-emphasized its value, particularly in testing young children in whom the skin reaction was frequently negative.

Technic.—Peshkin recommended desiccated pollen powder. Since we have seen a few severe local reactions with this method we have prepared serial dilutions of pollen extract for preliminary conjunctival testing. The strength of the material introduced into the conjunctival sac is progressively increased until testing is finally done with the dry powder. This method was also used by Cooke.

The dry powdered pollen is freed from impurities by passage through a two hundred mesh sieve, and stored in a moisture proof chamber, over calcium chloride. The precaution of keeping pollen dry is important, since otherwise molds may grow.

1. Prepare serial dilutions for conjunctival tests, using physiologic saline with 0.4 per cent phenol. Extract one gram of pollen in 10 cc. of carbolyzed saline, with frequent shaking at room temperature for from four to twenty-four hours. Filter through paper.

2. Label this extract with the name of the pollen and *dilution 1/10*. Dilute ten times with the same diluent, labeling it 1:100. In the same way prepare 1:1,000 dilution.

3. Never test with dry pollen powder if the skin reaction has been positive. Never test with dry pollen unless there have been two negative skin reactions.

4. Start with 1:1,000 dilution. Apply one drop with a medicine dropper, to the conjunctival sac. Wait five minutes. If the reaction is negative at the end of five minutes, apply 1:100 dilution in the same eye. After another five minutes if the reaction is still negative, apply a drop of 1:10. Finally, five minutes later, in the presence of a negative response, introduce a small portion of the dry powder.

5. To introduce the powder, dip the flat end of a wooden toothpick into the vial, lifting out as much powder as will cover the last one or two millimeters of

the pick. Evert the lower lid slightly by downward pressure on the skin and spill the powder from the toothpick onto the lower palpebral conjunctiva. Release the lid. The patient will at once experience a burning sensation, more so with ragweed pollen than with some of the others, which may be promptly relieved with pressure of the fingers or a cotton pledget over the closed eye.

6. Allow the powder to remain in the eye for two or three minutes. In the meantime, prepare a cotton brush, twisted on the end of a toothpick. At the end of the interval, evert the lower lid. Usually the yellow pollen will be found collected in a small strand of mucus, lying on the palpebral conjunctiva, near the inner caruncle. If this is touched with the cotton wisp, it adheres to the latter and may be readily lifted or sponged out. It is rarely necessary to wash the conjunctival sac with a few drops of physiologic saline.

7. A traumatic inflammatory reaction is seen in the mucosa, even in the absence of positive reaction. This is usually more pronounced in the lower part of the ocular and palpebral conjunctivae and usually extends to the caruncle. The traumatic reaction will subside within three minutes. An injection or erythema which persists more than five minutes after removal of the pollen powder or after the introduction of a drop of the solution may be considered positive.



Fig. 40.—The ophthalmo or conjunctival test. A one-plus or low-grade positive ophthalmo reaction. (Acknowledgment for this series of drawings, to M. Murray Peshkin, from *The Journal of Allergy* 6: 425, 1931.)

The five minute reading may show merely redness of the caruncle as compared with that of the other eye; more often redness of the mucosal surface of the lower lid and the adjoining ocular conjunctiva. The redness may extend through the major portion of the ocular conjunctiva, may in pronounced responses be accompanied by vascular dilatation and congestion and chemosis in extreme cases. A severe reaction may be followed by edema of the lids.

Since these pronounced reactions are neither necessary nor desired, the preliminary testing with serial dilutions enables the examiner to avoid them, by observing a definite positive reaction when present, with one or another dilution. This having been established, further testing is superfluous.

8. The reaction having been determined, it may be quickly controlled by the instillation of a drop of dilute adrenalin solution. For this purpose a mix-

ture containing 4 cc. of 1:1,000 adrenalin with sufficient saturated boric acid solution to make 15 cc. may be used. One drop suffices in most cases, although it may be repeated several times if necessary. This solution causes slight burning which is immediately relieved by pressure on the closed lids.

Several who have written on the subject state that adrenalin or cocaine solution may be used to control the reaction. Aside from the possibility of

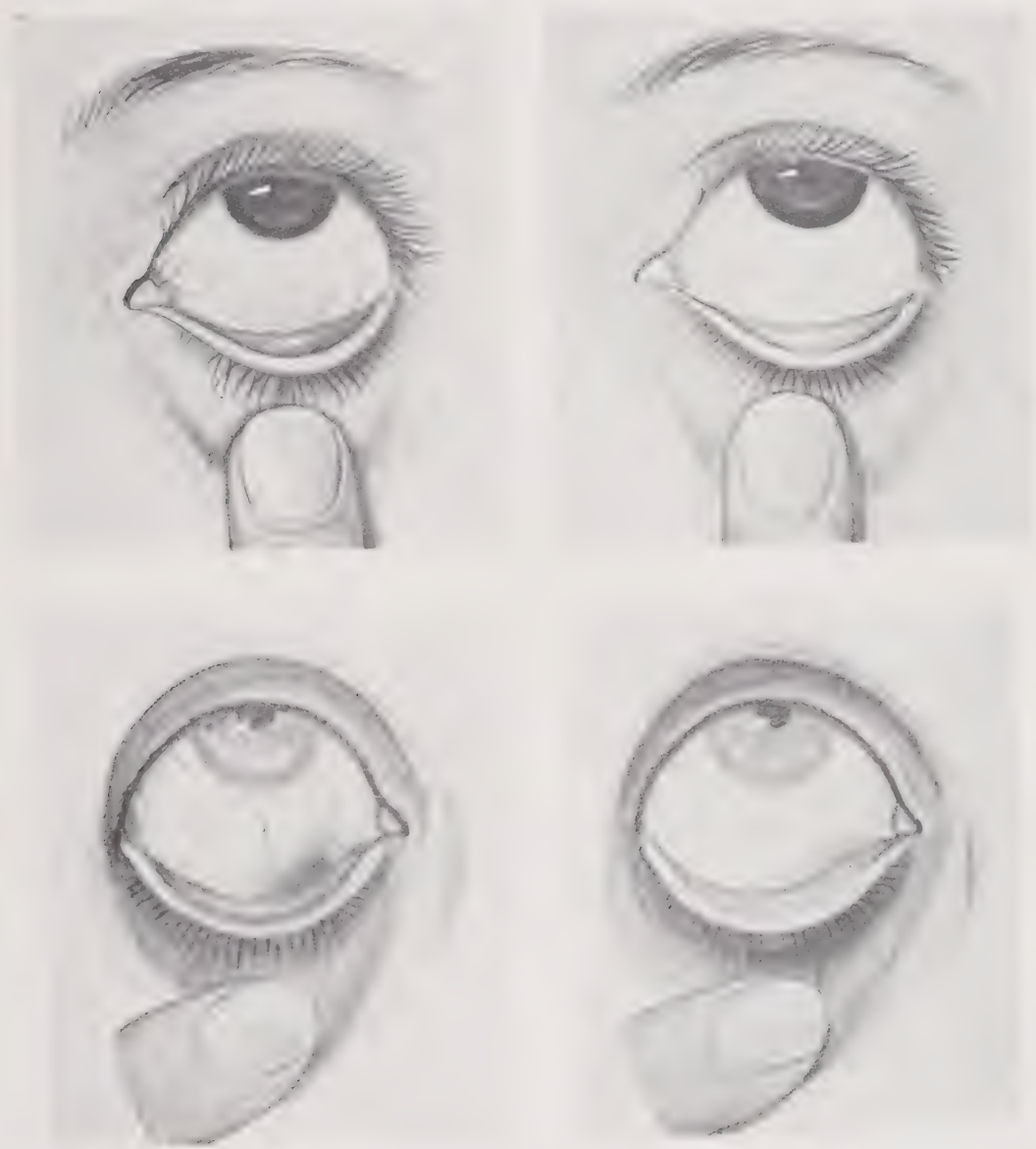


Fig. 41.—Two plus conjunctival reactions. Upper left: positive reaction, which clears up entirely after local application of adrenalin eye drops (upper right). Lower left: "blotch" type reaction which does not clear entirely after epinephrine (lower right). Peshkin terms this resistance to epinephrine, a "positive epinephrine test, indicating potential or etiologic sensitization."

cocaine sensitization, anyone who has used it once will not use it again if adrenalin is available, since the resulting mydriasis is as embarrassing to the examiner as any strongly positive local reaction.

Discussion.—The dry pollen conjunctival test was recommended by Peshkin in 1926 for the diagnosis of pollen allergy in those cases failing to give positive cutaneous reactions. He divides positive reactions into four groups

Conjunctival congestion persisting more than five minutes after removal of the dry pollen from the conjunctival sac is regarded as positive. In the one plus reaction there is moderate congestion of the sclera and palpebral conjunctivae, especially the lower, with slight redness and swelling of the caruncle.

In the two plus reaction the scleral redness is more diffuse and more intense. Vessels stand out more clearly. The three plus reaction is but a further exaggeration of these phenomena, while in the four plus there is chemosis of the conjunctiva and caruncle. The chemosis rather than the redness is the diagnostic feature of the four plus reaction. The sclera may appear jelly-like and the cornea may appear to be sunken in, below the raised borders of the sclera.

Rarely there is a delayed reaction appearing within 12 to 24 hours. I have seen one such case whose immediate reaction was no stronger than one plus but in whom on the following day there was moderate chemosis and generalized redness and edema of the eyelids. This lasted for 48 hours. Peshkin states that this is more likely to occur in patients suffering with vernal catarrh. My case was one of simple hay fever.

Peshkin also describes a rare phenomenon which he terms ophthalmographia. In it, any and all pollens appear to cause positive ophthalmic reactions. This differs from the traumatic congestion appearing after application of the dry pollen in that it persists for a long period unless controlled with epinephrin, while the latter disappears within five minutes. He likens the hyperirritability of the ocular conjunctiva in ophthalmographia to that of the skin in dermographia.

Peshkin emphasizes that the conjunctival reaction should not be attempted if the skin reaction is positive. This is true if one limits one's self to the dry pollen test. Reactions are likely to be too severe. He states that only the dry pollen test should be used since dilution of the pollen even to one part in twenty as an extract, invariably gives a negative reaction.

Our experience has been different. We often observe positive reactions to 1:20 dilution and not infrequently to 1:200 or even 1:2,000. Therefore, if skin tests for some reason have not been applied, the conjunctival test should be started with a dilution of 1:1,000. If this is negative, a drop of 1:100 extract may be applied to the conjunctiva. This still being negative, 1:10 may be applied. If this fails to cause reaction the dry pollen may be introduced into the conjunctival sac.

If the dry powder alone is to be used, a preliminary skin test should be performed in duplicate. One occasionally sees, in duplicate testing, that one reaction is negative, the other positive. One might therefore be misled by a single negative scratch test.

The positive ophthalmic reaction is promptly controlled with epinephrin solution. Peshkin recommends 1:1,000 solution and adds the caution that if 2 or 3 applications do not clear up the reaction it is well not to continue giving it because of resultant blanching of the skin on and below the lower lid. We find this not a problem when using the higher dilution of adrenalin, described above.

Peshkin recommends as a control test in the other eye, the introduction of a small amount of dry pine pollen. He states that he has never seen a positive ophthalmic reaction to pine pollen. Of course such a reaction could conceivably occur but other pollens may then be substituted. We have seen several cases with positive conjunctival reactions to pine pollen. In practice we use no control test in the other eye.

With two negative scratch reactions it is safe to proceed directly with the dry powder pollen test. We have had one case which was an exception to this rule. A man with hay fever during the elm season gave two negative scratch reactions to elm. We then did a dry powder ophthalmic test on the same day. The following day both scratch reactions were strongly positive, delayed, with swelling and erythema about three centimeters in diameter, the tested eye was red and the lids were swollen, edematous, the eye being almost closed. Curiously,



Fig. 42.—Three- and four-plus reactions. Diffuse injection (upper left) fails to at once respond completely to epinephrine (upper right), a "positive epinephrine test." Chemosis (lower left) indicates four plus. This also failed to clear up at once with epinephrine.

the conjunctival reaction had also been negative on the day of test. Here were two true delayed positive reactions, one in the skin and one in the eye. The patient was given coseasonal treatment with elm pollen extract with excellent results. During the next three succeeding years he has reported in with the onset of symptoms, has had coseasonal treatment, with excellent results each year. It is of interest that he usually has a rather pronounced delayed sub-

cutaneous reaction at the site of treatment. The arm becomes rather tender, slightly reddened and swollen over an area about two inches in diameter at each point of injection of 1:5,000 extract. This reaction evolves slowly over a period of about twelve hours, persisting for twenty-four to thirty hours. This again corresponds with the delayed positive reaction in the skin and conjunctiva.

Such a reaction is certainly very unusual but if it is to be completely avoided one would have to wait until the day following skin testing before testing in the eye.

There appears to be some variation in the intensity of the reaction to pollens, depending upon whether or not the pollen to which the individual is sensitized is in the air. I have occasionally done conjunctival tests on patients whose symptoms occurred during the ragweed season and who theoretically are allergic to ragweed, obtaining negative tests out of season, but clear-cut positive reactions during the season. The skin reaction does not appear to vary as much as the conjunctival in this regard.

Waldbott appears to have been the first to suggest this. He states, "even in fall hay fever patients, who are potentially sensitive to timothy inasmuch as they give positive tests to timothy but do not show clinical sensitivity, the reactions to ragweed were stronger during the time when timothy was in the air." This has diagnostic importance since if, preseasonally, one finds a suspected pollen negative to the dry powder pollen conjunctival test, this negative diagnosis may not be conclusive until it has been repeated during the season, when the patient is actually having symptoms. If, then, the reaction is positive the patient may be given coseasonal treatment.

According to Fineman the responsiveness or delicacy of the conjunctival reaction is between that of the scratch test and the intracutaneous. Given a stated series of dilutions, and progressing from more dilute to more concentrated, the endermal test will show up earliest, the conjunctival next, the dermal or scratch last. Therefore, those who employ intracutaneous pollen testing may have infrequent need for the conjunctival test.

We rarely find it necessary to test endermally with pollen extracts. Endermal tests are done with foods and other inhalant extracts which are usually not as strongly allergenic as pollen extracts. But in our experience, pollen allergies will react to scratch tests with 2 per cent extract in most instances, if they suffer from pollinosis. Although occasionally we test endermally, our usual pollen procedure is the scratch test followed in case of doubt by conjunctival tests with those pollens which may still be under suspicion. If the scratch test has been positive the conjunctival need not be done. If it has been negative and, because of the season of the year at which the patient has symptoms, a particular pollen is still under suspicion, conjunctival tests are done. If more than one are indicated, two tests may be done at one sitting, using the two eyes successively. If the first test is positive, the other eye is not used on that day, not because of the severity of the reaction in the first eye, but because adrenalin drops have been given.

If the scratch test alone is used the conjunctival test applied in conjunction with it enhances diagnostic accuracy. I cannot state from experience whether this would do so if endermal tests were used routinely. In our own work conjunctival tests are routine in those cases in which positive skin reactions do not coincide with the times of onset and offset of symptoms, and in those cases in which more than one plant pollinates at the same time and several have given positive skin reactions.

This latter is especially true during the tree pollinating season. The fact that a pollen reacts positively in the skin does not necessarily indicate that the individual will have symptoms therefrom. A surprisingly large proportion of ragweed sensitized individuals will also give positive skin reactions to one or more of the grasses even though they have no symptoms during the grass season. This is even more true of tree pollens. A positive pollen reaction, therefore, does



Fig. 43.—Positive conjunctival reactions. Upper left, diffuse blotchy injection of the nasal half of the ocular conjunctiva. Center right: vascular dilatation only, a one-plus reaction. Note that the mild reaction is usually more pronounced near the inner canthus. Lower right: four-plus reaction with slight chemosis. There need not necessarily be intense congestion accompanying the edema.

not necessarily indicate the cause of trouble. If a person reacts to two tree pollens both of which are usually in the air at the same time, the conjunctival test will often give information as to which extract should be used therapeutically.

With the routine which we employ, conjunctival reactions will sometimes be positive while the dermal test has been negative.

Experience has taught that one may reach a pretty definite conclusion regarding therapy when one finds a negative scratch and positive conjunctival reaction. These are mild allergies who often skip a season as far as pollinosis is concerned. Since there is thus a possibility that the patient will not have symptoms during the season, we do not customarily recommend preseasonal desensitization to this group. Instead, the patient is directed to await the onset of symptoms. If symptoms do not supervene no treatment is necessary. If they do, coseasonal treatment is given, usually with satisfactory results.

It becomes obvious that a comparison of the character of the skin and conjunctival reactions gives information concerning the proper treatment.

As stated above, it is possible those who routinely use endermal tests find the ophthalmic reaction superfluous. Walzer states, "It is unusual to find an adult patient with hay fever, who is more sensitive to the ophthalmic than to the intracutaneous test. There are, nevertheless, definite exceptions to this rule."

It may be that endermal pollen tests are necessary in certain sections of the country, especially where pollen counts are extremely high. A patient highly sensitized to ragweed will probably have symptoms both along the Atlantic Seaboard and in the central states. One mildly sensitized might have symptoms in the latter region, on account of the extremely high exposure to pollen and yet be symptom free or relatively so east of the Appalachian Highlands. Therefore, in those sections where pollen prevalence is extremely high and where it is important to recognize the very mildly sensitized, endermal testing might be desirable.

The ophthalmic test has a disadvantage that only one or two test allergens may be used at a time. However, with the routine as described above, only a few such tests are usually needed. An outstanding advantage of the test is that the allergen is applied to a mucous membrane, a surface corresponding to that which reacts in the actual disease.

The dilutions (1:10, 1:100, 1:1,000) are made in physiologic saline to which 0.4 per cent phenol has been added. The potency of this type of extract is not as permanent as that of the glycerosaline extracts. Extracts should therefore be kept at ice box temperature and renewed every three or four months.

The conjunctival test is also coming into general use as a diagnostic procedure preliminary to serum administration. Persons sensitized to horse serum customarily give positive conjunctival reactions to 1:10 dilution in saline. The undiluted serum may be used, but is sometimes irritating. Since it is of utmost importance that serum sensitization be recognized prior to the administration of any horse serum preparation, the routine procedure in testing for allergy thereto should consist of (1) scratch test with undiluted serum or diluted 1:10; (2) conjunctival test; (3) if these have been negative, endermal testing, first with 1:10 and then with undiluted serum (see Serum Disease).

Passive transfer in the conjunctiva.—Sherman, Feldman and Walzer have shown that the mucous membrane of the ocular conjunctiva may be passively sensitized. After the instillation of 2 per cent butyn, 0.1 cc. of the serum to be

tested was injected into the mucosa of the ocular conjunctiva. Subsequent testing was done by contact application, as in the usual conjunctival test. Specific positive reactions were observed. Following positive reactions a period of refractoriness in which positive reactions could not be obtained to any allergen often appeared, lasting as long as a month.

Passive Sensitization of the Rectal Mucosa and Other Tissues

Gray and Walzer have passively sensitized areas of the rectal mucous membrane, following which the allergic reaction could be induced following either oral or rectal administration of the antigen. The reaction consisted of edema, hyperemia and increased mucus secretion, with pruritus, burning, a sense of fullness and desire to empty the bowel. Since the reaction occurs within a few minutes after ingestion, one must assume that the excitant reached the sensitized rectal area through the blood stream. Walzer, Gray, Strauss and Livingston (1938), using the rhesus monkey passively sensitized various internal tissues with high titer human serum. They then observed local tissue response to intravenous injection of antigen. The mucosa of the entire gastrointestinal tract below the esophagus, the peritoneum, spleen and uterus all appeared susceptible to local passive sensitization. Liver, lymph glands, voluntary muscles, and subcutaneous tissues did not.

Sherman, Kaplan and Walzer have passively sensitized the nasal mucosa.

Nasal Reactions

Occasionally after the application of dry pollen powder to the ocular conjunctiva the patient will react with paroxysms of sneezing. This usually accompanies a positive "ophthalmo." However, we have seen persons whose conjunctivae appeared to be nonreactive since the ophthalmo reaction was negative but in whom the etiologic diagnosis was based entirely on the resultant paroxysms of sneezing. Only one of several pollens tested caused this, and treatment with this pollen extract relieved symptoms.

Nasal contact test.—In nasal allergy, the nearest we can come to reproduction of the natural phenomenon is the introduction of the suspected substance directly onto the nasal mucosa. Kirkman did this a hundred years ago. Blackley and Dunbar used it as a test procedure. Duke (1925) suggested it as a routine test. However, he made certain modifications, in an effort to avoid too intense reactions. His procedure consisted in spraying 1:1,000 pollen extract into the nose. The positive reaction consisted in sneezing, swelling of the nasal mucosa and increased nasal secretion, in other words a mild attack of hay fever of short duration.

Duke did not limit himself to the study of pollens. He had the patient inhale from any of a variety of substances to be tested, noting whether sneezing or other symptoms resembling hay fever or asthma supervened. As an example he described a carpenter troubled with nasal and bronchial symptoms while at work. When he inhaled from a bag of birch wood shavings he had a violent attack of sneezing. The shavings of several other kinds of wood caused no symptoms. Duke observed similar reactions to feathers, furs, perfumes, cedar oil, turpentine and smoke.

Efron and Penfound (1930) proposed the nasal test as a routine diagnostic procedure, more reliable than either dermal or endermal skin tests. Their work was done entirely with pollens. Using a De Vilbiss (No. 36) powder blower, they blew a small amount of dried pollen into one side of the nose. The tests were

done outside of the pollen season, when the patient was symptom free. Blowing the dry powder into the nose promptly caused suffusion of the eyes, especially the homolateral eye, slight burning and tingling in the nose and in more pronounced cases tingling pains at the vertex or occiput, slight increase of mucus in the nose and one or two sneezes. If the pollen was nonallergenic for the particular patient, symptoms subsided within a few minutes. If it was allergenic, hay fever symptoms of varying severity ensued. Most sensitized patients reacted within a few minutes, although there were some who experienced delayed reactions, symptoms appearing after as long as fourteen hours.

As soon as definite symptoms indicative of sensitization appeared the nose was irrigated with saline until all pollen was washed out, after which it was sprayed with ephedrin solution. As a rule, symptoms were of short duration, although the investigators described some cases which lasted for several days. One person experienced hay fever for two weeks following the test.

Just as there is no absolute correlation between skin test and conjunctival reaction, there is none between skin test and the nasal contact reaction. In 20 per cent Efron and Penfound observed negative skin tests but positive nasal reactions. In these the nasal reactions were shown to be true positives. They also observed positive skin reactions with negative nasal response. In these the skin test was falsely positive. This occurred both dermally and endermally. The pollens used were giant and short ragweed, marsh elder and cocklebur. False positive skin reactions were especially frequent with marsh elder. These four pollens are biologically closely related. As a rule, a positive ragweed reaction is considered as related to positive cocklebur or marsh elder reactions, and treatment with ragweed usually controls sensitization to the other two. However, with the nasal contact test they observed one patient who reacted to cocklebur only. In this case obviously treatment with ragweed would not be as logical as treatment with cocklebur extract. Species-specific sensitization has previously been discussed.

Following the report of Efron and Penfound the writer procured a De Vilbiss powder blower. However, the amount of powder delivered through the blower was so much greater than that to which any one would be normally exposed, that I experienced great hesitancy in trying it. I did try it with orris root, not blowing the powder directly into the nose, but, instead, out the window, with the patient who was at the window, sniffing the cloud of powder as it passed his nose.

In the meantime Rudolph and Cohen suggested a different method of testing which they had applied to persons with vasomotor rhinitis, whose skin reactions had been negative. Among 500 persons with nasal symptoms they found 34 per cent with seasonal allergic rhinitis, 58 per cent with perennial allergic rhinitis, diagnosed by positive skin reactions, and 8 per cent with perennial rhinitis without positive skin reactions. The difficulty of allergic diagnosis in the absence of positive skin reactions in this 8 per cent is obvious. For these they prepared a local intranasal test as follows:

The allergen is sprinkled on a pledget of cotton slightly moistened with saline and inserted on a probe against the mucosa of the middle turbinate and nasal septum. A control probe with saline is applied in the opposite nasal chamber. Contact is maintained for twenty minutes, after which the pledgets are removed. Immediate mechanical reaction which occurs in all cases consists in suffusion of the eyes and irritation of the nose. There may be burning, tingling and even pain over the bridge of the nose with some mucous secretion

and occasionally a sneeze or two. Examination of the nose at this time shows a highly congested mucosa. If the individual is not sensitized symptoms subside in several minutes. In the presence of allergy typical vasomotor rhinitis on the tested side will ensue. Most patients react within twenty minutes. The longest reaction interval was 12 hours. In the presence of a positive reaction the congested mucous membrane becomes pale, edematous and there is an increased mucous secretion.

Reactions are controlled with tampons of 1 per cent ephedrin or by irrigation with warm normal saline. Occasionally the reaction is prolonged, with nasal obstruction which in one case lasted an entire week. Only one substance is tested in each twenty-four-hour interval. Twenty-two patients were so studied. In 19, from 1 to 4 positive reactions were observed in each patient. Substances used consisted of dried epidermals of goose, chicken, duck, canary, cattle, dog, cat, horse, rabbit and wool; cottonseed, flaxseed, kapok, mattress dust, orris root, pyrethrum, glue, grass and ragweed pollens.

In 8 of the 19 patients Rudolph and Cohen obtained relief amounting to from 50 to 90 per cent following treatment based upon positive intranasal reactions.

The possibility of prolonged reaction lasting a week or more is as obvious a disadvantage in the technic employed by Rudolph and Cohen as that used by Efron and Penfound. Furthermore, the mechanical irritation necessary in the execution of the Rudolph-Cohen test appears to me to be a factor which should be avoided if possible.

At the suggestion of Hansel* we have used the following procedure which has been so satisfactory and so free from untoward reactions that it has become routine.

Powder puff test.—(1) For testing, use dry powdered allergen, either the pollen powder or the purified powdered allergen manufactured for scratch testing.

(2) Do not attempt to test in the presence of active symptoms of nasal allergy, since a positive reaction will not necessarily increase symptoms already present, and, in the presence of objective symptoms there is no way by which one can distinguish between positive or negative response. In the absence of acute nasal symptoms, the test may be applied.

(3) Twist a wisp of cotton loosely on the end of a toothpick, leaving evenly frayed edges, a miniature powder puff.

(4) With nasal speculum, inspect the nasal mucosa, selecting the side for testing which appears more nearly normal. A reacting nasal mucosa is pale, sometimes almost pearly, more or less edematous, often with increased mucus.

(5) Dip the dry powder puff into the test substance. A small portion remains attached to the frayed ends of the puff. Having selected the side of the nose for testing, instruct the patient to close the other side. Hold the puff at the nasal orifice while the patient takes a short sharp sniff, not too deep. The powder promptly disappears from the puff, aspirated into the nose where it is deposited on the nasal mucosa.

The degree of contact is more nearly that which one would normally experience. Hence the name, *powder puff*. As a rule, the immediate or mechanical reaction is slight, possibly a sneeze, rarely a sense of stuffiness or pain. If sneezing ensues there may be slight temporary conjunctival congestion.

*Hansel, French: Personal communication.

After five minutes, the nasal mucosa is again inspected. In a positive reaction there may be beginning edema with pallor and increased secretion. There may be sneezing, rhinorrhea or even lachrimation. At least fifteen minutes is allowed before the examination is completed, when the nasal mucosa should be again inspected. Occasionally there are delayed reactions, so that no more than two or at most four tests should be done in a twenty-four-hour period. If four are done, two on each side, and delayed reaction occurs, they must be repeated separately.

The record of each test should include description of the nasal mucosa before application of the puff; after five minutes and fifteen minutes; the occurrence of sneezing, itching, stuffiness, rhinorrhea or lachrimation, especially after five minutes; and when possible, in positive cases, record of smear eosinophile count, at the height of the reaction. A positive reaction with visible turbinal edema may be delayed, reaching its height only after an hour or two.

If the test is positive an ephedrin nasal spray may be applied, with quick subsidence of symptoms. The test is of no value in the presence of active symptoms.

We have used it routinely for three years, using allergens which have been positive and negative by skin test, and we have seen no embarrassing reactions, none that have lasted more than a few hours.

Discussion.—The nasal contact test has the obvious advantage that we are reproducing the actual disease, by natural methods. A disadvantage is that only a few tests may be done at a time, but since a thorough study of the frank allergic requires several days, this is not a material disadvantage. Only those inhalant allergens which come under special suspicion are used. The fact that skin reactions, either scratch or endermal, have been positive does not control the selection of powder puff tests. I have seen three and four plus endermal reactions or even scratch reactions to allergens such as house dust, feathers, orris root, pyrethrum and tobacco show entirely negative by powder puff and vice versa. This is important, since if the direct application of orris root to the nasal mucosa does not cause symptoms in a case of nasal allergy one need not put the patient to the bother of avoiding orris root or being hyposensitized to it. As a consequence our routine is to test by the powder puff method with the more common inhalant allergens such as dust, feathers, orris root, tobacco, silk, pyrethrum. Occasionally, others such as horse dander, rabbit hair, cat hair, etc., are used. The decision as to avoidance or treatment depends upon comparison of the results of skin test and nasal contact with the clinical symptoms. We do not use the test routinely with pollens, since the conjunctival test is simple.

This technic differs from that of Rudolph and Cohen in that they employed nasal contact only in cases which failed to give positive skin reactions.

Natural allergens. If this test is employed as a routine procedure, and if the number of patients studied is great, the expense of using purified allergen powder becomes not inconsiderable. For this reason it is desirable to employ cruder allergenic substances, which incidentally are more nearly like those with which the patient normally comes into inhalant contact. Pure powdered orris root may be obtained from the drug store. If the patient suspects a particular cosmetic powder this may be used. House dust may be used as such after preliminary sifting to remove large particles. Tobacco may be pulverized and used as such. The same procedure may be used with old feathers and kapok which have become brittle. Pyrethrum powder may be obtained from a drug

house. The prepared insect powders should not be used because some are naturally irritating. Suspected inhalant allergens such as rabbit hair, horse hair, dog hair, cat hair, silk, cotton fibers, flax, orris root, feathers may be mounted between concave wire meshes and appropriately labeled. These are held to the nostril while the patient sniffs. All should be in as near their native state as possible. Thus raw silk is preferable to treated silk and feathers obtained directly from the fowl are preferable to processed feathers, ready for the pillow.

Nasal intramucosal test. We have seen that the conjunctival mucosa may be passively sensitized following intramucosal injections. Dean and his co-workers have applied intramucosal tests on the inferior turbinate, injecting the allergen as in an endermal test. They found positive reactions similar to those of the skin, some even going on to wheal formation. Response was usually observed within from fifteen to thirty minutes. Positive reactions were often accompanied by nasal symptoms such as obstruction, increased secretion and sneezing. In this test as in the skin and conjunctival tests delayed reactions are observed, coming on several hours after testing. It is especially interesting to note that both inhalants and ingestants such as wheat, egg and milk reacted positively in the nasal mucosa. Dean found positive intramucosal reactions to substances which had given negative skin reactions.

Contact allergic coryza.—Forman (1934) looks upon the idiosyncratic response of the nasal mucosa to atopens and nonatopens as comparable to atopic and contact reactions of the skin. Some substances causing dermatitis give positive atopic skin reactions, while others react only by contact or patch test. In the same way substances producing vasomotor rhinitis which cannot be proved to be atopens by skin test may cause mucous membrane responses which appear to be specific. This includes especially certain volatile oils, perfumes, odors of alcohol, gasoline, frying foods, formaldehyde, smoke, etc. In such cases intentional inhalation of the suspected excitant may facilitate diagnosis.

Bronchial contact test.—Stevens has carried the application of the test allergen to the limit of directness by having the patient inhale weak solutions of the test substances. After studying a sufficient number to draw conclusions he discontinued the method because of the occasional severe asthmatic reaction, sometimes lasting several days.

He found that those asthmatics who were dermally insensitive or nonreactive usually did not react to direct application by inhalation. But in those in whom the skin reaction was positive the inhalation test was often positive, even though it might not be the same substance which caused the positive skin reaction. In approximately one-half of those in whom the inhalation reaction was positive the intracutaneous reaction to the same substance had been negative. In one-half, the positive skin reaction corresponded with the positive inhalation reaction. It is interesting that in food allergies, with asthma, the asthmatic reaction could be produced by inhalation of an extract of the allergenic food.

It would appear that with inhalants as with foods, the skin reaction is not infallible but gives about 50 per cent of the desired information; that direct inhalation is more reliable, but that the method is not desirable as a routine because of the occasional severe response.

CHAPTER XXII

THE PATCH TEST

This is primarily the dermatologists' contribution to allergy. The patch test is not new, having been introduced by Jadassohn in 1894. It was popularized in Europe by Bruno Bloch, in this country by Sulzberger and others. Cooke (1916) and Spain (1922) employed the procedure in the diagnosis of ivy poisoning with the application of an alcoholic ivy extract to the skin.

Technic.—A suitable area free from eruption is selected for testing. This is usually the back or the arm but if these areas are involved with dermatitis other regions of the skin such as chest, abdomen or thigh may be used.

Apply the test substance directly to the skin, preferably in that state in which it normally is in contact. The strength employed should be one which experience has shown is harmless for normal skin. A soluble substance may be dissolved in water or the material may be suspended in olive or almond oil. A single drop of the test material suffices.

Cover the applied material with a one inch square of cellophane. Cover the latter with a square of adhesive enough larger to assure sealing the test site for a sufficiently long period.

Write the name of the test substance on the adhesive.

If several tests are to be made, they may all be applied in a row which is then covered by a single long strip of adhesive, the names of the test substances being written over each.

Allow the substance to remain in contact with the skin long enough to determine the reaction. The time interval varies. Twenty-four or forty-eight hours usually suffices. However, since the reaction occurs much more rapidly at times, the patient should be instructed to report to the office at any time if itching or other discomfort becomes pronounced. If he cannot do so, he should remove the plaster himself, preserving it to bring with him later. This latter point is especially important if several tests have been done and the plaster has been correspondingly labeled.

There is a ready prepared patch test adhesive plaster, *Elastopatch** which is of appropriate size and has a cellophane disc already applied to the adhesive surface. This is often convenient when only a few tests are being done or when they are being made on the rounded surface of the arm, where the adhesive tabs on each side serve to hold the plaster in place. An equally good simple patch may be made using 1½ inch waterproof adhesive, cut diagonally into a diamond shape.

An alternative method consists in applying the test substance when it is in liquid or paste form to a small square of linen about one-fourth inch square. This is next covered with a one-inch square of cellophane and finally with adhesive. This has a very definite advantage, that there is usually a zone free from reaction between the linen and the adhesive, the area where the skin was in contact with cellophane. This is especially desirable since a surprisingly large proportion of persons are allergic to adhesive. One can usually recognize a positive reaction one-fourth inch square as easily as one a full inch square. The surrounding free zone is advantageous. With this method application is also

*Duke Laboratories, Inc., Long Island City, New York.

easier, since the cellophane may first be attached to the adhesive and then fitted squarely over the piece of linen. A control site must be used with a square of the same linen or cotton.

Adhesive substitutes. Grobniak and Walzer have suggested a method for use in cases sensitized to adhesive. They employ cellophane discs 2 or 3 centimeters in diameter to cover the test site, which are sealed to the skin around the



Fig. 44.—Application of the patch test. Circular patches at left, of bird's-eye cloth, sealed with frisket. Frisket is applied in a circle, using the mouth of a small bottle for application. Test material is placed in the center and both are covered with cloth. Soap patches at the right are with adhesive plaster. A drop of the test material was applied either directly to the skin or on a small square of cloth; then it was covered with a square of cellophane and, finally, with adhesive slightly larger than the cellophane.



Fig. 45.—Ready prepared patch test material of the adhesive plaster type and with good adhesive quality. The cellophane protection is incorporated in the patch material, "Elastopatch." This may be applied on arms, legs, back, or elsewhere.

circumference with a special collodion or liquid adhesive* said to be non-allergenic. The transparency of the cellophane permits observation of the reaction during the course of its development. A rather heavy cellophane (600 weight) is used. Nonmoisture-proof cellophane should be used since the authors have reported contact dermatitis due to moisture proof cellophane.

*Johnson and Johnson.

U. S. P. collodion is not suitable since it contains benzoin, castor oil, balsams and essential oils which may serve as allergic excitants.

Although the special collodion so far appears to be nonallergenic, one could, as an emergency procedure, use ordinary collodion.

To protect the cellophane cover, a sleeve of stockinette bandage is rolled over the arm and held in place with elastic sleeve garters.

After reading, the collodion is removed with ether or acetone.

Other methods of patch application such as bird's-eye cloth and frisket or rubberized cloth and "Duo liquid adhesive" are described under "adhesive dermatitis" (Chapter LXVIII).



Fig. 46.—When dermatitis involves the back, the patches may be applied elsewhere. When a large number of materials must be tested they may be placed in rows and covered with long strips of adhesive. For subsequent identification it is well to write the name of the material being tested on the adhesive, over the appropriate site.

Plant oils in acetone are now available commercially* and make a more satisfactory mode of testing than the use of pollen, leaves, etc. A drop of the extract is placed on the skin and spread over an area of approximately 1 cm. and allowed to dry. The drops should be placed about 5 cm. apart, and as many may be used as can be placed on the back at one time. These drops are not covered. Since the extract may be rubbed off the skin by the clothing, making it difficult to find the spot one or two days later, some method of identification must be used. Shelmire marks squares with a flesh pencil, while we place a dot of carbol-fuchsin stain beside each spot. Either of these methods will indicate the location of the drop for several days. Tests made in this way are read in the same manner as those before mentioned.

Site of testing. Sulzberger has observed that certain skin areas may be more reactive than others. Thus, when dermatitis involves the face, patch tests are more likely to be positive if applied to the face or to the "V of the neck." This is the V-shaped area below the jaw, customarily exposed, especially in women.

*H. L. Graham Laboratory, Dallas, Texas.

When dermatitis of the face is presumably due to contact allergy, and contact tests applied to the back, arm or elsewhere, have failed to indicate the etiologic agent, they should be repeated on the V of the neck. This suggests the possibility of other associated areas. As emphasized by Sulzberger a contact test should not be construed as finally negative until it has been repeated in an area that has previously been involved with the dermatitis.



Fig. 47.—Types of positive patch tests. Upper: papular dermatitis without vesiculation after 24 hours' contact. Lower: vesiculation after 24 hours.

Record of reactions.—As with the dermal or endermal skin test, reactions may be classified as early or late. An early reaction usually does not appear as rapidly as the early scratch or intracutaneous reaction. An early patch reaction may occur within from two to four hours, with vesiculation or even bulla formation. Delayed reactions appear after many hours, even after two or more days. It is less explosive and takes on more the nature of a chronic eczematous lesion as contrasted with the earlier vesicular one.

Bruno Bloch classified patch test reactions as follows:

Grade I: Simple erythema.

Grade II: Erythema, edema, formation of nodules.

Grade III: Pronounced erythema, edema, abundant nodules, beginning mild vesiculation.

Grade IV: Confluent vesicles.

Grade V: Destruction of the epidermis, progressing in some cases to necrosis.

This classification is entirely acceptable, but the time element should also be indicated. Vesiculation or bulla formation within four hours is a more strongly positive reaction than after twenty-four hours.

Delayed reactions. Patches are usually left in contact with the skin for 24 to 48 hours, at which time readings are made. Delayed positive reactions may appear after a longer interval (following removal of the test substance). The positive reaction may appear after four or five days or even a week. Readings should therefore be repeated over this interval. Positive reactions appearing ten days or more after first patch application probably indicate beginning sensitization at the end of the usual incubation period. This response has been observed in primula and rhus reactions.

Selection of test substances. Any suspected substance may be employed in patch testing, provided one is certain that it is not a natural irritant. Strong acids or alkalis or other substances which normally damage the skin should not be used. Allergy to soap is quite common. Soap as a rule is rather strongly alkaline. A soap paste allowed to remain in contact for some time will cause a Grade I reaction, or stronger, in any skin. Obviously, therefore, soap as such should not be employed in the patch test. Furthermore, one does not customarily leave soap lather in contact with the skin. One's endeavor should always be to approximate as nearly as possible the natural contact. In testing with soap, therefore, one should make a weak soap emulsion for contact application. This should be dilute enough that on control skins it does not cause dermatitis within the twenty-four-hour interval. This general principle will apply with all patch test substances.

These instructions having been applied, there is no limit to the materials that may be used. These may vary from sawdust from some particular wood, through paper, cellophane, ointments, to pure metals such as nickel and synthetic chemicals such as paraphenylenediamine (Ursul), the black dye so commonly used in the preparation of leathers, cloths, and the like.

The fact that dermatitis from clothing may be due not only to the cloth but to the dyes and finishes explains failure at times to recognize the offending material. If silk is suspected it is not enough to patch with silk or with simple uncolored silk cloth. The actual material being worn by the patient must often be used. This even comes to the point where, when black stockings are suspected, it is not enough to test with any black stockings, but with the particular black stockings under suspicion.

For discussion of test materials used routinely, see Table LXX, Chapter LXIX.

Testing with therapeutic materials. Knowledge of contact dermatitis has been of material assistance to the dermatologists who have found that individuals may be allergic to some of the local medicaments. Ayres and Anderson report four cases of sensitization to such a simple local remedy as Whitfield's ointment. This contains 2 parts of salicylic acid, 4 of benzoic acid, to 30 of benzoinated lard. One may become sensitized to any of the three constituents.

For testing, the authors used three substances: salicylic acid, 2, petrolatum, 30; benzoic acid, 4, petrolatum, 30; and benzoinated lard. They observed positive reactions at one time or another to each of the three.

They emphasize that the idiosyncrasy was not manifested so much as dermatitis venenata as by an exacerbation of the previously existing condition. Whitfield's ointment is used principally in the treatment of the fungus infections of the skin. Persons who develop allergy to the ointment will first appear to improve as a result of the fungicidal effect. Later the original lesion will return and appear to spread. Withdrawal of the ointment results in temporary improvement which is again followed by exacerbation due to new growth of fungi.

Dermatologists of wide experience often start treatment with a weak ointment in order to make sure first that the individual is not sensitized thereto. Ayres and Anderson remark that if dermatologists would use diagnostic patch tests before the application of curative remedies, they could, in the absence of sensitization, proceed at once with the stronger remedies, thereby obtaining better final results.

Sulzberger and Morse have reported contact dermatitis due to wool fat. Lanolin is often used as a base for ointments. Therefore, those with dermatitis who do not respond adequately to treatment may be allergic to wool fat and should be tested thereto.

Testing with plant extracts.—Early studies of dermatitis due to plants were directed especially to those which produced this reaction in the larger proportion of the population, poison ivy, poison oak, poison sumac and primula. Other plants not usually considered allergenic may produce contact dermatitis. Thus, dermatitis has been found due to dog fennel by Rowe; to bleeding heart by Harville; to chrysanthemum by Pilot; to tansy by Greenhouse and Sulzberger; to marsh elder by Huber; to helenium by Balyeat and Rinkel.

Shelmire* routinely tests with oils from 56 different plants (see Table XIX). This includes those plants with which farmers and others in east Texas are more likely to come in contact. Sixteen of them have been found allergenic. He states that contact dermatitis from plants (excluding ivy) was found due to parthenium, bitterweed (dog fennel) and burweed marsh elder in about 95 per cent of cases. Cocklebur, giant and short ragweed, and sneezeweed are less frequent offenders. Rare excitants include hackberry tree, Amoor privet hedge (snuff bush), cotton, Shasta daisy, sorghum cane, Forney hay (a local grass), Sudan grass. Sunflower and corn are somewhat more important.

He finds 25 or 30 cases, annually, allergic to parthenium, 10 to 15 to bitterweed, and 5 to 10 to burweed marsh elder. All routine tests were done with 1:20 dilutions.

Pollen oils.—According to Brunsing and Anderson the first systematic reports of dermatitis caused by ragweed were those of Hannah (1918), and of Sutton (1919). Sulzberger and Wise reported positive patch reactions in 1930. In 1931 Brown, Milford and Coca reported that an oily substance in the plant was responsible for the contact dermatitis. This was to be distinguished from the protein fraction responsible for hay fever and asthma.

Pollen dermatitis usually affects the eyelids, neck and exposed surfaces above the collar line, and the hands and ankles.

*Shelmire, J. Bedford, Dallas, Texas. Personal communication

In performing patch tests for ragweed dermatitis Brunsting and Anderson found that ripe, unwashed pollen gives as strongly positive a contact reaction as that caused by the leaf or stalk of the plant. The pollen is moistened slightly with olive oil. Scratch or endermal tests with water soluble ragweed allergen in 13 cases showed positive reactions in but 2. In a few of the scratch tests, although there was no early reaction, local dermatitis appeared after three or four days, which they interpreted as of the same significance as a positive patch test and due to the fact that pollen and pollen oil had probably not been adequately removed from the skin.

TABLE XIX.—SHELMIRE'S TEST PLANTS

SCIENTIFIC NAME	COMMON NAME
<i>Centaurea americana</i>	American thistle; sultana star thistle
<i>Aster multiflorus</i>	Many-flowered aster
<i>Cynodon dactylon</i>	Bermuda grass
<i>Helenium tenuifolium</i>	Bitterweed; fennel; yellow dog fennel
<i>Rudbeckia hirta</i>	Black-eyed susan; niggerhead
<i>Amphichayris dracunculoides</i>	Broomweed
<i>Diodia teres</i>	Rough buttonweed
<i>Croton capitatus</i>	Capitate croton; hogwort
<i>Kallstroemia maxima</i>	Greater caltrop
<i>Eupatorium serotinum</i>	Boneset; late-flowering thoroughwort
<i>Xanthium speciosum</i>	Cocklebur; Clotbur; Sheepbur
<i>Melilotus alba</i>	White sweet clover; honey clover; tree clover
<i>Froelichia floridana</i>	Cottonweed; prairie froelichia
<i>Syntherisma sanguinalis</i>	Crab grass
<i>Croton monanthogynus</i>	Single-fruited croton
<i>Lespedeza frutescens</i>	Bush clover
<i>Heterotheca subaxillaris</i>	Camphor daisy; camphorweed
<i>Erigeron philadelphicus</i>	Fleabane; daisy fleabane; skevish
<i>Ambrosia frifida</i>	Giant ragweed; horseweed; wild hemp
<i>Rumex crispus</i>	Yellow dock; curled dock
<i>Iva angustifolia</i>	Narrow-leaved marsh elder
<i>Thelesperma gracile</i>	False coreopsis
<i>Solidago serotina</i>	Late goldenrod
<i>Marrubium vulgare</i>	Hoarhound; houndshene
<i>Monarda punctata</i>	Horsemint; perennial sandyland sage
<i>Acan illinoensis</i>	Illinois mimosa
<i>Gaillardia pulchella</i>	Indian blanket; showy gaillardia
<i>Vernonia baldwinii</i>	Ironweed
<i>Chenopodium botrys</i>	Jerusalem oak; feather geranium
<i>Sorghum halepense</i>	Johnson grass
<i>Chenopodium album</i>	Lamb's quarters; white goosefoot
<i>Gaura parviflora</i>	Lizard's tail; velvetweed
<i>Leptilon canadense</i>	Mare's tail; Canada fleabane
<i>Iva ciliata</i>	Rough marsh elder
<i>Aselepiodora viridis</i>	Oblong-leaved milkweed; silkweed
<i>Cassia chamaecrista</i>	Partridge pea; large flowered sensitive plant
<i>Amaranthus blitoides</i>	Prostrate amaranth; spreading pigweed
<i>Parthenium hysterophorus</i>	Santa Maria feverfew
<i>Amaranthus retroflexus</i>	Redroot pigweed; careless weed
<i>Cyceloma atriplicifolium</i>	Winged pigweed; tumbleweed
<i>Prionopsis ciliata</i>	Prionopsis
<i>Helenium microcephalum</i>	Sneezeweed
<i>Solanum elaeagnifolium</i>	Silver-leaved nightshade
<i>Aster exilis</i>	Slim aster
<i>Euphorbia marginata</i>	Snow-on-the-mountain
<i>Ambrosia elatior</i>	Short ragweed; wild tansy
<i>Hartmannia speciosa</i>	Showy primrose
<i>Helianthus annuus</i>	Common sunflower
<i>Aenida tamariscina</i>	Western water hemp
<i>Lactuca ludoviciana</i>	Wild lettuce; western lettuce
<i>Artemisia mexicana</i>	Wormwood; Mexican mugwort
<i>Verbena officinalis</i>	Wild verbena; European vervain
<i>Achillea millefolium</i>	Yarrow; milfoil; Thousand-leaf
<i>Kuhnia glutinosa</i>	Prairie false boneset
<i>Salsola pestifer</i>	Russian thistle; saltwort; windwitch
<i>Chrysanthemum coccineum</i>	Pyrethrum

Coca finds that oil extracted from the leaf of the plant causes a stronger skin reaction than that from dried pollen. He states that the oil in the leaf deteriorates rapidly following drying and storage.

Stroud finds some patients reactive to the oil of short ragweed and not to that of giant ragweed. He finds multiple sensitization common in contact dermatitis. Perennial dermatitis may be due to the action of several seasonal factors. For example, one patient with ragweed dermatitis had a similar eruption in the winter, due to contact with wool.

Dust oil.—It would appear that, in contact dermatitis due to an organic substance, the latter is less frequently protein, more often an oil. In pollen dermatitis, patch testing with an aqueous "protein" extract may be negative while an extract designed to retain the oil constituent is positive. Stroud observed persons with dermatitis of exposed skin who had exacerbations during periods of house cleaning and at seasons when contact with house dust was increased. Patch tests with suspected dusts gave little or no reaction. However, an oily fraction from house dust caused strongly positive reactions. Normal persons were negative. Treatment with dilutions of the oily extract gave relief.



Fig. 48.—Dental plate patch test material. Artificial dentures are made with a variety of materials. These may be obtained in small flat squares which are easily applied in patch testing. A patient allergic to his own denture may be tested with several others, a negative one being selected for a new denture.

Stock test material. The diversified examples mentioned above illustrate the wide variety of possible etiologic contact agents. The discussion also brings out the fact that, as in the case of house dust, unless appropriate measures are taken to isolate and concentrate the contact factor, false negative reactions may lead to erroneous conclusions. A certain number of plant factors cause symptoms in a sufficiently large proportion of patients, so that it is worth while for the physician who does any large amount of work in this field, to develop stock testing solutions with the commoner substances. This may be done easily by making acetone extracts of leaves or other parts of the plant (ivy, ragweed, etc.), extraction being carried out for twenty-four hours. The acetone is then filtered off and evaporated to about one-third or one-fourth of the original volume. This is kept as a stock patch test solution.

Contact stomatitis.—The patch test is applied on the skin. It should not be inferred that contact allergy involves the skin only. It may affect the mucous membrane. This is strikingly brought out in the observation by Ratner of stomatitis due to sensitization to dental plates. He reports three persons whose

stomatitis was definitely shown due to contact with a new synthetic plate known as hecolite. Vulcanite had been used previously without sensitization. An interesting feature was that with the plates removed at night the mouth became less irritated by morning. There was a diurnal variation. The point of special interest as far as the patch test is concerned is that Ratner found that if the dental plate was applied directly to the skin of the arm as in the ordinary patch test procedure, a positive reaction resulted.



Fig. 49.—Positive patch test to artificial denture. This was made of vulcanite. Testing with several similar preparations showed negative reaction to hecolite. A new denture was made using hecolite. There has been no recurrence of stomatitis.

Shelmire found that he could produce an eruption on the mucosa of the mouth by keeping the membrane as dry as possible while poison ivy was held in direct contact with the membrane. He believes that the mucosa is not usually involved because the antigen is washed off the surface by the secretions.

This would indicate that in some instances at least, if contact allergy is suspected as responsible for symptoms on a mucosal surface, testing may be done on the skin.

CHAPTER XXIII

THE LEUKOPENIC INDEX

A fall in the total leukocyte count accompanies anaphylactic shock. Widal and a number of French authors have described a fall in the total white count accompanying acute allergic episodes. These as a rule were not sufficiently violent to be termed shock, but the symptoms were usually acute and severe. Leukopenia occurred not only after food ingestion but also from inhalation of excitants.

From his study of these more or less explosive allergic responses Joltrain concluded that, to be of significance, the leukocytes must show a drop of at least 2,000 cells per cu. mm. from the preexisting level.

Widal, Abrami and Iancovesco had proposed a test for liver function based upon the Widal hemoclastic crisis test. Blood pressure, white count and clotting time determinations were made upon the fasting patient. He then ingested 200 grams of milk. In the presence of functional liver damage, the postprandial leukocyte count fell, the blood pressure fell and the clotting time became prolonged. Widal stated that of the three observations the leukocyte response was the most important and could be used alone as a gauge.

Vaughan found this procedure unreliable as an hepatic function test, but observed that in persons known to be allergic to milk, there was a resultant drop in the total white count, irrespective of the presence or absence of liver damage. The possibility that a leukopenic response was not due to hepatic injury, but to milk allergy was obvious. This suggested the idea that the same test might be employed as a diagnostic procedure in food allergy provided it could be demonstrated that the response was specific, occurring only to those foods to which the individual was sensitized. Further study indicated that this was probably true. A person sensitized to milk reacted to its ingestion with leukopenia, while other nonallergenic foods in the same individual did not cause a leukopenic response. The same appeared to be true for other foods.

Feeling that the leukocyte response might be used as a diagnostic procedure, the writer developed the leukopenic index.

Criticism.—Early observations indicated a reliability greater than that of the skin test for foods. The latter, in parallel control series showed 65 per cent accuracy, against 81 per cent for the leukopenic index. Findings were based on blood counts calculated from the counting of ten squares on the hemocytometer chamber, or a minimum of 200 cells. That is, in the presence of leukopenia, if 200 or more cells were not totalled in the ten squares, more squares were counted to reach at least this minimum. This standard was selected in part on the basis of the observation of Bryan, Chastain and Garrey, that counts could be made within an accuracy of about 1,000 cells, with this technic.

Denny (1937) reported greater reliability when 16 squares are counted. Hill and Nethery; Loveless, Dorfman, and Downing; Brown and Wadsworth (1938), concluded that accuracy within 1,000 cells could not be assured unless 32 squares are counted. When this was done Hill found the leukopenic index to be of diagnostic value, while the other authors concluded that any apparent correlation between leukocyte response and food sensitization disappeared, and that the test is therefore without value in allergic diagnosis.

Since the publication of these criticisms, Vaughan and Thomas have undertaken a study of 1000 leukopenic indices to foods, known to be allergenic or nonallergenic in each instance, and counting 32 square centimeters in each enumeration. Analysis of the first 459 index determinations showed 79.6 per cent correspondence with the presence or absence of symptoms, as against 62.5 per cent correspondence between skin tests and symptoms.

Technic.—The patient reports, fasting. The test should be started before nine-thirty since it requires two hours and there is evidence that in the afternoon there is normally a wider fluctuation in the white count, both fasting and postprandial, than in the morning.

Two fasting total white counts are made at 30 minute intervals, 32 one millimeter squares being counted for each determination. The patient next eats the food to be tested. One hour after completion of the test breakfast, a third white count is made. A final count is made thirty minutes later.

For comparison there are available four counts, two preprandial and two postprandial. The mean of the two fasting counts is taken as the basic count. If there is a wide discrepancy between the two, especially if the second is lower, the possibility exists that the first count was abnormally high, due to the "random activity" of coming to the office. In this event the second fasting count, made after 30 minutes' rest is more likely to be correct than the mean of the two counts. If either of the subsequent counts falls 1,000 or more below the fasting mean, the index is considered positive, indicating allergy to the food being tested.

Occasionally a case is observed in which all postprandial counts are low, but none quite reaching 1,000 drop. This is often found to indicate a positive reaction.

Sometimes the leukopenic response occurs later than an hour and a half after the last count. Therefore, if the last count shows that the curve is falling, subsequent counts should be made at half hour intervals, until the direction of the curve is finally determined.

Since there are a number of variables in the determination of the leukopenic index, it is highly important that as many of them be controlled as possible. For this reason great accuracy is required in the performance of the white count. Thorough mixing of the cells in the pipette is requisite. If hand shaking is employed, this should be done for three minutes each time. The Feder pipette shaker in our experience adequately distributes the leukocytes within sixty seconds. This is the only one of the available mechanical pipette shakers which in our experience adequately accomplishes this purpose.*

The patient remains seated throughout the test except when he crosses the street to procure his test breakfast. However, on his return he remains seated at least thirty minutes, usually forty, before the next white count is started. He is not permitted to smoke.

In recording the test a notation is also made as to whether symptoms develop during it or afterwards, and a similar notation is made on the following day, covering possible delayed reactions.

Only one food at a time is customarily tested and only one test is done each day. An average portion serves as an adequate amount. Examples are one glass of milk, three slices of toast, two eggs, one cake of chocolate, a side dish portion of green peas, one or two lamb chops, etc.

*Manufactured by A. S. Aloe Co., St. Louis.

Bureau of Standard pipettes are not required, but the same pipette, counting chamber and cover slip are used throughout the determination. Thirty-two squares (16 on each of two double counting chambers) are counted each time. Each chamber always has the same cover slip. An automatic counter greatly simplifies the task.

Until recently, few extensive investigations of the reliability of total leukocyte counts have been made since Students' studies (1907). Many have written upon the reliability of white counts, but few on that of white counting. Conclusions have ranged all the way from those of Ponder, Saslow and Schweizer (1931) who believe that there is little fluctuation in total white counts through the day and that apparent changes have been due to defective technic; to the conclusion of Shaw (1926) that physiological oscillations in the size of counts during the day are too great to be attributed to faulty technic.

Bryan, Chastain and Garrey (1935) have run a large series of simultaneous white counts which they then analyzed by modern statistical methods. Their study takes into consideration all the possible factors of variation such as filling and dilution in the pipette, proper filling of the counting chamber, settling of the cells "by chance" on the ruled field of the counting chamber, variations in calibration of the appliances, and methods of obtaining the sample from the finger. This last is of utmost importance. A sharp clean stab should be made. They recommend a sharp cataract knife. Blood should flow freely and squeezing of the finger should never be employed, since this expresses tissue juices which hasten clotting. The first five drops should be wiped away since they may contain leucocytes which are "in-storage" in adjacent capillaries. Subsequent drops are found to be identical with venous blood. In other words it is important to avoid obtaining capillary blood.

Blood flows more freely if the hand has been warmed, but this is not necessary provided more than five free flowing drops have been obtained. Clotting may be prevented if necessary by wiping each drop from the finger with a gauze sponge slightly moistened with 5 per cent oxalic acid followed immediately by wiping with a dry sponge. The patient should be cautioned not to put the finger to his mouth.

At least forty seconds should be allowed before taking the drop for counting, during which the initial vasoconstriction gives place to active vasodilation.

Ponder, Saslow and Schweizer concluded that, assuming proper technic in obtaining blood, dilution and delivery into the chamber, the chief factor influencing accuracy was that of chance distribution on the counting chamber. They believed that 800 cells must be counted each time before this factor could be made negligible.

Bryan, Chastain and Garrey found that if 10 square millimeters be counted (5 on each side of the chamber), with the blood diluted 1 to 20, the average error in counting was ± 241 , ± 35 cells per cu. mm. of blood. The standard error of analysis was ± 303 , ± 46 , the probable error ± 204 , ± 31 . In other words, the accuracy of white counting thus performed with careful technic is within 1100 or 1200 cells (three times the standard deviation). They found this true with total white counts varying from 3,000 to 15,000.

It should be noted that in the interpretation of the leukopenic index as described by the writer, a total variation of 2,000 is allowed for, represented by 1000 increase and 1000 decrease over the fasting level. This therefore pro-

vides approximately three times the standard deviation reported by Bryan et al., on each side of the mean.

As stated above, more recent work by Hill, by Loveless and by Brown indicated that, for accurate counting within an error of 1000 cells (not 2,000 as just mentioned), 32 squares should be counted. Since this obviously will increase accuracy it is a procedure which should be adopted when feasible.

The standard deviation.—"The constant which has been adopted by biometricians to measure in absolute terms the degree of scatter or dispersion of the variates is called the standard deviation. It is the same quantity which in theoretic mechanics is called the radius of gyration. It is a parameter of the variation curve, representing a distance on the x axis such that if the total frequency were concentrated at that point and connected by a rigid bar with the mean, the system would have the same rotational properties about the mean in a frictionless medium as would the whole distribution in its actual form if it were rotated in the same medium about the mean as an axis. Roughly, three times the standard deviation on either side of the mean will include all the variates."

"A standard has to be devised that will be applicable to different kinds of problems. This standard is a measuring-rod by which the difference between any sample and the mean of the series can be measured. These differences are also called deviations from the mean, and the standard measuring rod is called the standard deviation. The standard deviation is defined as
$$\sqrt{\frac{\text{sum of squares of deviations from mean}}{\text{Total number of observations}}}$$

"For any series that can be presented by a normal curve, twice the standard deviation, measured from the center or mean, will exclude at the extreme left and right ends of the series, a total of roughly 5 per cent of all samples (2.5 per cent at each end)."

"Three times the standard deviation, measured on each side of the mean, gives roughly the upper and lower limits of a normal curve, or more accurately, includes all except one out of 370 measurements."

"A standard error of a mean is simply a standard deviation of a set means."

Sources of technical error. Garrey and Bryan have reviewed the literature on normal white cell variations. Their article should be consulted for details and for study of the conflicting conclusions reached in nearly every phase of the investigation which might have some bearing upon the performance and interpretation of the leukopenic index.

They list the three chief technical sources of error in white counting as (1) failure to procure samples representing systemic blood, (2) failure to mix properly the diluted sample in the pipette and (3) failure to count enough cells to minimize the inequalities of distribution on the field of the hemocytometer. The first of these may be adequately controlled following puncture of the finger or ear by waiting for the initial vasoconstriction to pass off and using late drops after secondary vasodilation. A very sharp instrument causes minimal contraction of the arterioles, more active hyperemia.

If a minimum of 800 cells are counted, error due to uneven distribution is practically eliminated.

Leukocyte counts of over 10,000 per cu. mm. are observed in normal persons, but as the white count rises above this figure, the chance of its occurrence in normal individuals decreases rapidly. This has therefore been accepted as the arbitrary upper limit of normal white counts.

Effect of age. The leucocyte count of the newborn is high, ranging even up to 45,000. In the majority it lies between 10,000 and 25,000. After the first two months there is a tendency toward gradual decrease during the first two years. Throughout infancy and early childhood there is a tendency toward wide fluctuation.

The limits of normal white counts are generally accepted as: for six months of age, 10,000 to 15,000; one year, 9,000 to 14,000; the second year, 8,000 to 13,000. During the first two years the average normal white count is 11,000. Lymphocytes predominate during the first two years, with lymphocytes and neutrophils about equal at age two.

At about five years the average total count is 10,400. From age eight to eighteen it is 8,300 and from age nineteen to thirty it is 7,400. In the first of these three age groups the limits of normal variation are 6,000 to 15,000; in the second 4,500 to 13,500 and in the third 4,500 to 11,000. This includes 95 per cent of individual counts.

In adults the normal range has been found by various investigators as between 3,500 and 15,600, using different subjects with counts taken at different times. This obviously is not based upon serial white counts taken on one person over short time intervals as is done in the leukopenic index.

Diurnal fluctuation.—Much has been written concerning periodic or cyclic fluctuation in the white count during the twenty-four hours. The major evidence indicates that there is no clearly demonstrable periodicity although very occasionally large and abrupt variations in the counts of normal individuals have been observed by all investigators. There is a definitely recognized tendency toward a higher total count in the afternoon than in the morning. When counting is carefully controlled and at least 800 cells are counted, it is most exceptional to observe sudden wide variations within short periods of time, unless an obvious cause such as heavy exercise, emotional excitement, etc., exists.

Activity.—The majority of counts at rest range from 5,000 to 7,000. Rest of an hour at any time of day appears to accomplish basal conditions as far as the white count is concerned. However, the zone of fluctuation of resting counts in the afternoon is definitely wider than in the morning, made so by an extension of the upper limit rather than the lower.

Comparisons of white counts, with the subject erect and supine, have given inconsistent results with different observers, with no definite conclusions reached as yet.

The majority of investigators report that "random activity" of one's ordinary routine does not cause a rise in white counts. Garrey and his collaborators believe that it does cause a slight increase.

Strenuous exercise definitely produces a leukocytosis. Examples are a 43 per cent increase in soldiers after a long march; white counts ranging from 14,200 to 27,700 in marathon runners, which still remained high two hours after the race; 200 and 300 per cent increase in football players after from eight to sixty minutes of play; 100 per cent increase following heavy gymnastics; and from 43 to 98 per cent increase following a 220 yard dash. The leukocytosis following a run of eight-tenths of a mile returned to normal in thirty minutes. A leukocytosis of 35,000 immediately after a quarter mile run and emotional excitement returned to 13,000 after 45 minutes.

Leukocytosis following strenuous exercise is accompanied by an increase in both lymphocytes and neutrophils. The former appear to increase as a result of increased lymph flow.

Leukocytosis increases progressively with the severity of work done. Leukocytosis accompanying exercise is not, as has been suggested, due to contraction of the spleen and consequent delivery of cells into the blood, since it

also occurs after splenectomy. It is not due to blood concentration since it has been shown that concentration could not account for more than one-twelfth of the leukocyte increase. The leukocyte shift may occur very rapidly. In one case it rose to 22,000 after a 100 yard dash which lasted less than eleven seconds. In another, leukocytosis of 35,000 followed a quarter mile run which lasted one minute. Blood samples were taken as soon as possible after this exercise. An increase up to 12,000 to 13,000 occurred within two minutes after twenty knee-bends. Return to normal occurred in fifteen minutes. Increases of from 19 to 43 per cent which followed weight-raising returned to normal within two or three minutes. A standard running exercise lasting thirty seconds showed an increase of 2,000 cells immediately at the termination of the exercise. The increase continued for from one to five minutes following which it receded more gradually. With mild exercise the return to normal is complete after fifteen minutes of rest. Following more vigorous running, recovery required thirty minutes.

Epileptic convulsions are followed by leukocytosis.

The question arises whether patients on whom leukopenic index determinations are being made should be kept under basal conditions, at complete rest through the experiment. As the test is done in the writer's clinic, the patient reports to the office at 9 A.M. and sits in the testing room. As soon as practicable the fasting counts are made. The patient then crosses the street to eat the test food. He returns to the office where the remainder of the test is completed with the patient seated in a comfortable chair. Almost invariably he has been sitting at least thirty minutes before the first postprandial count is made.

Drugs.—Adrenalin causes a pronounced leukocytosis with an increase in both neutrophils and lymphocytes. This may last an hour or two, occasionally as long as six hours, usually due to persistence of the lymphocytosis. The lymphocyte increase appears to be due to an increased lymph flow associated with stimulation to contraction of the lymph nodes. It may be that lymphocytosis accompanying strenuous exertion is due to increased adrenalin stimulation.

Food.—Some authors deny the existence of digestive leukocytosis while others conclude from their equally recent investigations that a low-grade leukocytosis accompanies digestion. Garrey and Bryan doubt the existence of a true digestive leukocytosis but admit the possibility of a postprandial leukocytosis. This implies the existence of leukocytosis during the process of digestion, but not due to that process. Other factors which might be responsible are increase in hydrochloric acid; heating, chilling and overdistention of the stomach; and psychic factors. Alcohol produces leukocytosis within an hour after ingestion.

Altitude. Climate appears to have no effect. High altitude usually produces leukopenia with absolute lymphocytosis. Acclimatization, with an increase in leukocytes, has been described.

Gestation. Leukocytosis occurs during pregnancy, at least in primiparae, which increases toward term. The leukocyte count at the onset of labor averages 17,000. It is greatest in primiparae and in severe prolonged labor.

Psychogenic factor.—Emotional upsets have been shown to cause leukocytosis. A case of hyperthyroidism under basal conditions had an increase from 7,000 to 18,000 following the suggestion of an operation. Leukocytosis

has been shown to accompany pain without infection, as in renal colic and stretching of the sciatic nerve over a tumor mass. Ten minutes of confusing oral examination produced leukocytosis. Persons under hypnosis have been made to react with leukocytosis accompanying suggested affective states such as joy, sorrow, rage or jealousy.

Affective leukocytosis probably occurs as a result of vasomotor changes which release leukocytes into the circulation from storage depots as described in the next section.

Capillary bed.—Changes in total white counts occur too rapidly and are of too great magnitude to be explained simply on the basis of formation and disintegration of the cells. Furthermore, many instances of leukocytosis fail to show the presence of new or immature neutrophils. The obvious question is, Where do the leukocytes disappear to and where do they come from so suddenly? Leukocytes normally accumulate in the capillaries of various organs. This capillary accumulation and storage has been observed frequently, has even been recorded in motion pictures. It appears to be especially active in the capillaries of the bone marrow, lungs, liver, spleen and intestines. Drops of blood obtained from puncture of an organ may show a higher count in the earliest drops, falling shortly to that which is normal for the circulating blood. The earliest represent leukocytes stored in the capillaries. This fact explains the need, when performing white counts on finger or ear blood, for obtaining spontaneous flow and for discarding the first drops. The early high counts represent cells sequestered in the tissue capillaries.

In anaphylactoid shock the lungs are found packed with leukocytes. Following the intravenous injection of bacteria leukocytes accumulate in the liver, lungs and spleen. They collect in the spleen following nucleic acid injection. The local accumulation of leukocytes in anaphylactoid reaction may be due to endothelial swelling. It has been demonstrated that specially stained leukocytes injected into the splenic artery or portal vein are removed by the liver; injected into the ear vein of rabbits and dogs they are removed in the lungs.

The evidence suggests that leukocytes are sequestered in the capillaries from which point they may be mobilized into the general circulation by circulatory changes, even such changes as accompany emotional upsets.

Undoubtedly the delivery of new-formed leukocytes from the bone marrow also plays a part at times, as does the delivery of lymphocytes from the lymph nodes. However, this can scarcely account for the sudden and relatively tremendous increases which sometimes occur. There is no unanimity of opinion concerning the mechanism of the circulatory readjustment which produces leukocytosis.

Although it was formerly suspected that leukocytes were very short lived, remaining viable in the circulation only for a matter of hours or three or four days, present evidence indicates a life of upwards of two or three weeks.

“Squier (1946) reported that the transitory leucopenia which followed the ingestion of food to which the patient is sensitive is accompanied by and may be due to an increased fragility of leukocytes. A later publication shows that leukocytes may be disintegrated in the test tube in the presence of reacting antigen and antibody. This work offers an attractive explanation for the leukopenia just discussed. It could occur rapidly enough and in sufficient amount to account for the changes found. Confirmation and further investigation may be very helpful.

Randolph (1947) states that certain allergic individuals who develop acute symptoms following the trial ingestion of food show a decrease of eosinophiles coincident with the clinical reaction and, as the symptoms subside, develop a delayed eosinophilia. It is seen most clearly in cases of acute reaction of short duration, and the entire response is not commonly observed during the first hour after feeding. This is not a constant finding, but there is no such response after the feeding of compatible foods.

Conclusions

Many of those who have worked with this method have found it of definite value. They believe that it is much more dependable than the skin test, and that it can be carried out with sufficient accuracy to make the results reproducible if the technical details are properly cared for. Conceding that much greater accuracy is obtained by counting 32 square millimeters, Loveless and associates and Brown and his co-workers still do not agree that the method is a reliable test for food allergy. Others who have used it over a period of years are still of the opinion that it is a useful, dependable method.

It must be said that the majority of those doing allergy have not continued to use the method. This may be due, in part, to unsatisfactory experience with it, but, with many, there is the conviction that, while it may be sufficiently dependable, it is time consuming, requires technical accuracy which cannot always be found in office assistants or technicians, and the same information may be obtained by dietary manipulation which, while slow, may yield entirely reliable results.

CHAPTER XXIV

DIAGNOSTIC STUDY OF THE NASAL SECRETION

Eosinophiles

The finding of eosinophiles in the nasal secretion is not new. According to Hansel this was first done by Bizzozero in 1887. Its occurrence in asthma, nasal polyposis and spasmodic coryza was recognized about 1890. However, it was not until 1927 that rhinologists became seriously interested in it as a phase of the problem of allergy.

Eyermänn (1927) found that 72 per cent of 59 cases with nasal allergy showed eosinophiles in the nasal secretion. Only 9 per cent among 42 similar but nonallergic nasal cases showed eosinophiles. Hansel, and Kahn and Stout among others have written on the subject. Hansel, in particular, has made most extensive clinical studies and described the characteristics and significance of the cellular elements of the nasal secretion.

Obtaining material.—Material is obtained by having the patient blow the nose directly on wax paper or cellophane. Glassine paper, used by pharmacists in the weighing of drugs, is inexpensive and of appropriate size and consistency.

The secretion from each side may be examined separately. Nasal allergy is practically invariably a bilateral affair, but since there may be a superimposed unilateral infection, the cytology may be different on the two sides.

If through noncooperation by children, or for other reasons, secretion cannot be obtained by blowing, it can often be removed in sufficient quantity for study, on an applicator, the cotton swab of which is then rubbed directly on to the microscope slide. We have occasionally had recourse to postnasal catarrhal mucus obtained either with a swab introduced through the mouth, or with the patient dislodging a specimen by hawking. This is rarely necessary. If the secretion is too scant, it may sometimes be stimulated by contact of a saline applicator against the turbinates. Sinus washings obtained by irrigation or aspiration may be examined cytologically.

Staining.—A thin smear is made on a clean slide and allowed to dry. Staining may be done either with Wright's stain or Giemsa's. Hansel prefers the Giemsa stain,* stating that it gives less false staining and, where a large number of smears are stained at one time, the individual slides do not require the exacting technic of the Wright method. Hansel's technic is as follows.

Fresh stain should be made up, from stock solution, each time. The latter is diluted 1 drop to the cc. of distilled water. About 1.5 cc. of stain is required to fully cover each slide. The stain remains in contact for 25 to 30 minutes, after which it is poured off and the slide is dipped into distilled water. A few drops of ethyl alcohol may be used to clear off excess stain. Placed on end, on filter paper, it dries rapidly. I prefer 45 minute staining, followed by 5 minute washing in tap water. For permanent preservation, a drop of balsam is applied and covered with the coverslip.

*Giemsa stain may be obtained from the Gradwohl Laboratories, 3514 Lucas Avenue, St. Louis, or from Akatos, Inc., 55 Van Dam Street, New York, N. Y.

Eosinophile granules appear reddish brown. Nuclei are blue. Neutrophiles show a clear violet cytoplasm. Masses of neutrophiles may take the eosin stain in excess in which case they closely resemble eosinophiles, but on careful examination it will be seen that true granules are not present.

Interpretation. Hansel emphasizes that one cannot determine the presence of allergic eosinophilia by estimating the percentage frequency of eosinophiles. Distribution in the mucus is often quite uneven, only certain portions showing larger accumulations of eosinophiles. A slide may show neutrophiles predominantly with only here and there a clumped mass of eosinophiles.

Clumping of eosinophiles is of diagnostic importance.

The character of the secretion usually gives some idea as to what one may anticipate in the cytology. A profuse watery secretion usually has very few cells of any kind. Eosinophiles may be found only after repeated examinations. The thick mucus which usually accumulates during the subsidence of an acute response may contain an abundance of eosinophiles. A yellow purulent secretion, usually indicating infection, usually contains chiefly neutrophiles although, not infrequently, eosinophiles are seen in a yellow secretion and may even predominate.

Since one should be interested not only in the indications of allergy (eosinophiles) but also those of infection (neutrophiles), the record of the examination should describe both elements. This may be recorded as relative percentages but as stated above, such record gives a false impression of accuracy. A truer representation of what one actually observes may be made with the scheme recommended by Hansel.

TABLE XX.—SCHEMA FOR RECORDING THE CYTOLOGY OF NASAL SECRETIONS

E + -	Few scattered eosinophiles
E +	Many eosinophiles—may be clumped
E ++, +++, ++++	Eosinophiles very numerous—large clumps
E +-, N +-, +	Few scattered eosinophiles and neutrophiles
E +-, N ++, +++, ++++	Few eosinophiles and numerous neutrophiles
E +, N +-, +	Many eosinophiles and neutrophiles
E +, N ++, +++, ++++	Many eosinophiles and numerous neutrophiles
E ++, +++, ++++, N +-, +	Eosinophiles very numerous—many neutrophiles
E ++, +++, ++++, N ++, +++, ++++	Eosinophiles and neutrophiles very numerous

Eosinophiles may be present in an allergic nasal secretion in the absence of symptoms. Again, they may be absent. Therefore one may examine the secretion in the absence of symptoms, but if eosinophiles are not found and there is still question as to the allergic etiology, repeated examinations should be made, and especially during periods of exacerbation.

Neutrophiles

An occasional neutrophile is a normal finding in the nasal secretion, not necessarily indicating infection. This is observed especially in older persons. In those cases in which local allergic symptoms are pronounced and there is nasal obstruction with stagnation, secondary infection may ensue, with resultant increased neutrophile concentrations. This is also true when there has been widespread destruction of ciliated epithelium, replaced by nonciliated cells. Here the secretion tends to stagnate and become infected. Stagnation and infection are especially likely to occur in the presence of allergic polyps. However, in polyps, eosinophiles are apt to be especially frequent along with the neutrophiles.

According to Hansel eosinophiles may be increased in ordinary acute coryza to such an extent as to suggest an allergic response, but, as acute symptoms subside, eosinophiles rapidly disappear. This is in contrast with allergic coryza where neutrophiles disappear gradually while eosinophiles usually increase.

So far as I know Hansel is the only observer who has emphasized the fact that even in the allergic response the neutrophiles are also increased. "In evaluating the number of neutrophiles in the secretion, one must take into consideration that the neutrophilic response is always greater than the eosinophilic response and that the number of neutrophiles usually outnumbers the eosinophiles about ten to one. A plus minus or a one plus number of neutrophiles represents about ten times as many eosinophiles. In a smear with four plus neutrophiles the field is completely covered with them."

Infection.—Depending upon the presence or absence of infection the cytology from the two sides of the nose may vary. When symptoms persist after the subsidence of the hay fever season, nasal smear examination aids one in determining whether infection or allergy is the continuing agent. Conversely, when there is obvious nasal infection and a question as to nasal allergy, repeated smear examinations during subsidence of the infection will eventually demonstrate whether an allergic factor also exists.

A single smear examination is rarely final. It should be repeated at different stages in the evolution of the nasal pathology.

Eosinophiles in the Blood

Randolph (1944) describes a method for determining the eosinophile count in blood. Such counts sometimes have an advantage over the differential, which shows only the relative percentage of eosinophiles.

Technic

Solution 1		Solution 2	
0.1 per cent methylene blue in		0.1 per cent phloxine in	
propylene glycol	50 c.c.	propylene glycol	50 c.c.
Distilled water	50 c.c.	Distilled water	50 c.c.

The final white blood cell diluting fluid is made by mixing an equal number of drops of Solution 1 and Solution 2 in a test tube. This remains usable for about four hours. Counts are made in the standard counting chamber. Ten or fifteen minutes is required for maximum staining of the cells. The granules of the eosinophiles stain brilliant red and the nucleus is green. The nuclear elements of all white cells take an emerald green stain.

CHAPTER XXV

PHYSICAL ALLERGY

According to Horton, Brown and Roth the first report of probable physical allergy was that by Bourdon (1866) who described urticaria and syncope apparently due to cold. The first classic description of urticaria from cold was that of Blachez (1872). In the ensuing forty years six writers described single cases of urticaria attributable to cold. In 1921-2 three groups of writers reported similar cases of what we now term cold allergy.

Duke's contribution.—Duke's first report appeared in 1924 and it is to him that we are chiefly indebted for our present knowledge of the phenomenon. Duke first suggested a relationship between allergic disease and this unusual response to physical agents; showed a close parallelism in the character of the reaction; recognized its occurrence in persons who were otherwise allergic or who had an allergic family history; demonstrated that mechanical irritation, heat, light and effort as well as cold could serve as excitants; described local and systemic responses which latter might occur in remote shock tissues or as a general reaction; described early and delayed reactions; developed effective therapeutic measures; and proposed the term *physical allergy*, which has since come into general use. Concerning the mechanism of the condition, he suggested among other possibilities that a histamine-like substance might be liberated locally. As we have seen, Lewis later showed the probable existence of such a substance.

When Duke made his early observations he believed that he was dealing with a very unusual condition. As his interest increased and he commenced searching for similar cases he became convinced that illness from the action of physical agents is not uncommon. During one year he observed over fifty such cases. Although Duke wrote voluminously on the subject, acceptance of his observations by other students of allergy was slow. In the ensuing ten years not more than a dozen articles appeared on physical allergy, aside from those contributed by Duke. These were chiefly case reports.

Improved testing technic. In 1932 we initiated tests for physical allergy in our diagnostic routine. The procedure was quite complicated and rather messy. The response or reaction to testing was hard to evaluate. We remained in some doubt as to the practical value of the procedure as a routine diagnostic measure.

In 1929 Horton and Brown reported their study of six cases of allergy to cold. They followed the systemic response to cold applied locally, when the circulation from the chilled area was intact, and when it was impeded by a tourniquet. Their study therefore was made with the application of cold to an extremity. This differed very materially from Duke's testing technic.

As a result of this earlier study, Horton, Brown and Roth in 1936 described their new method of testing for cold sensitization. This is much simpler and more easily applied. Following the adoption of this simplified technic, we have employed it as a routine test procedure. We have inaugurated a similar test for heat sensitization, based upon the same principle. Since these

tests have been in use in our clinic as a routine procedure, we have discovered a number of cases in which physical allergy plays an unsuspected part.

In describing the diagnostic procedure, it seems desirable to mention both the older technic of Duke and the more recent one of Horton, Brown and Roth.

Older Test Methods

Cold test.—The patient is tested for cold allergy by vigorously rubbing ice over chest, back and arms. Ice cubes are too small and melt too rapidly. If the source of supply is an electric refrigerator, water is frozen in the trays with the partitions removed. The "old fashioned" bulk ice is preferable. If the patient is sensitized to cold he will respond with urticaria, asthma, sneezing or whatever the particular symptom in his case. The length of application of the ice rub depends upon the speed with which symptoms become manifest. Theoretically one should continue until symptoms appear. In practical work, if symptoms have not appeared within three or four minutes the rub is discontinued and at least ten minutes are allowed for the appearance of symptoms.

This test requires practically complete disrobing since the melted ice trickles down the sides, back or abdomen with consequent wetting of the clothing unless it is removed practically down to the knees. It involves wetting of the sheet on the testing table and the use of a rubber sheet beneath. Soon the patient is either sitting or lying in a pool of water.

Except possibly in the summer time there is always the risk of catching cold after the chilling of so large a body surface. The patient must therefore be carefully dried. A light protective olive oil massage should be applied, to stimulate the circulation in the skin. It is well also to apply body talc which does not contain orris root.

Heat test.—The patient is exposed under a 1500 watt nitrogen lamp with an appropriate reflector, the lamp being at a distance of approximately 18 to 24 inches from the skin. The ordinary heat therapy lamp of this type does very nicely.

Heat is applied to the chest or back or both for a period of ten minutes or until the patient manifests symptoms of reaction.

Contrast test.—As Duke has emphasized, the allergic response to heat or cold is not necessarily to fixed or absolute degrees thereof but may be to changes in temperature. Therefore, if the patient has not responded allergically to the cold or heat test, he may do so when the two are alternated. Here the sudden change is the excitant. Therefore the two tests described above may be alternated successively. Sometimes this causes reaction when neither alone will.

Control of reactions.—If a person has reacted to heat or cold Duke finds that the application of the opposite excitant (cold or heat) will quickly terminate the reaction. If therefore a person responds to the application of cold, with allergic symptoms, heat is applied in the manner described above. I have seen angioneurotic edema inaugurated by the cold test, which did not respond to subsequent heat application. Duke also states that epinephrine is efficacious in the control of reactions. This also is not always true in my experience.

Newer Test Methods

Cold test.—The patient's hand and part of the forearm are placed in water at about 9° C. or 48° F. (approximately electric refrigerator temperature) for six minutes. During this period the skin blanches locally. After removal from

the water the local pallor changes to redness, slight edema, and this is followed by an increase in the local temperature. This is characteristic of a positive reaction. The systemic positive reaction usually develops later, in from three to six minutes after removal of the hand from the cold water. It may affect any of the shock tissues and may even cause constitutional reaction with fall in blood pressure, rise in pulse rate, vertigo or even syncope. Untoward symptoms may be counteracted by dipping the hand in warm water.

The procedure, then, involves exposure of one hand and part of the forearm in cold water for six minutes, followed by a six minute observation period for local and the possible systemic responses. If after the six minute observation no symptoms have appeared, the same procedure is repeated except that a tourniquet is applied above the elbow and left in place through the second six minute period of cold exposure, and for two or three minutes thereafter. The tourniquet is then released. The subsequent observation period is again six or more minutes. Horton, Brown and Roth observed that with the tourniquet subsequent reactions were more severe and lasted as much as three times longer than when the tourniquet was not used. The test should first be applied without the tourniquet.

They found that without the tourniquet reactions occurred as a rule within four to six minutes after withdrawal from the cold environment. With the tourniquet, reaction was more rapid, usually appearing in from one to two minutes after its release.

Following removal of the hand from cold water both systolic and diastolic blood pressures usually fall in sensitized individuals, followed by a rapid rise, so that at the end of six or eight minutes they have returned to the initial level. The pulse rises as the blood pressure falls and returns to normal almost as rapidly.

We have found a one gallon earthenware crock preferable to metal or enamel dishes since the former is not as good a heat conductor and retains the cold longer. The crock, about three-fourths filled with water, is kept in the electric refrigerator ready for use.

In the event of a severe reaction, not controlled by dipping the hand in warm water, a tourniquet may be applied above the elbow, thereby theoretically at least terminating delivery of *H-substance* into the systemic circulation.

Heat test.—This is applied in the same manner, first without tourniquet and later with tourniquet, the water in the crock being as warm as the patient can comfortably tolerate, usually around 104° to 108° F. (40° to 42° C.).

Other Tests

Actinic test.—Testing for sensitization to the sun's rays may be done either in the normal way, with exposure of more or less of the body surface to sunlight, or with the ultraviolet lamp. There are many makes of the latter, and a single lamp varies in the amount of ultraviolet which it delivers, depending upon its age and the care that has been taken of the quartz glass. Therefore one cannot designate a stated time for exposure during the test. The amount which, with the particular lamp in use, will result in a mild erythema in the ensuing twenty-four hours is a proper exposure. With an active quartz mercury-vapor lamp this is usually from two to three minutes, at 36 inches from the skin.

Variable amounts of the body may be exposed. One arm suffices although it is our custom to expose the upper half of the body, with the half below the belt protected as a control.

The author has devised a *dodging screen* which is applied in a manner similar to that used by photographers in the process of *dodging*. This consists of a thin board or cardboard containing a series of parallel slots approximately 1 inch by 3 inches, all separated by about 1 inch. Another cardboard which is either superimposed or built in, slides across the slots. At the beginning of the test only the first slot is left uncovered by the second board. After 60 seconds the sliding board is withdrawn, to expose a second slot. One minute later the third slot is exposed, etc. Assuming five slots, the first exposes an area of skin one inch by three inches to ultraviolet light for a total of five minutes; the second four minutes; and so on to the last which represents a one minute exposure. Here again the actinic activity of the individual lamp must determine the maximum length of exposure.



Fig. 50.—Results of testing to ultraviolet rays. Oblongs are cut in a cardboard. These are covered with another board which is moved down, at one-minute intervals, to expose successive areas. The normal sunburn response depends upon the ultraviolet machine being used. Readings are made within twenty minutes for urticaria and at twenty-four hours for sunburn and vesiculation. Exposures in the figure range from one minute to five minutes. Normal response.

Exposure through the slots may be made on the arm, thigh, back, chest or abdomen. The entire body is covered except those sections exposed in the slots.

With the dodging frame one may determine not only local allergic response in the skin but also the individual skin tolerance to the burning effect of ultraviolet. The local allergic response may be early, in which case it customarily appears as urticaria; or it may be late or delayed, presenting the picture of an eczema or dermatitis. The exposure is usually not sufficient to produce systemic symptoms of actinic allergy such as asthma, allergic coryza, migraine or angioneurotic edema.

If one prefers to use normal sunlight for testing, one should bear in mind, as Duke has emphasized, that the response to the direct actinic rays of the sun varies with the time of year and with the moisture in the air. A person

may experience actinic allergy in the summer but not in winter, or when the humidity is very low but not when it is high. Obviously in this case the determining factors are the intensity of the sun's rays and the effectiveness of the filtering blanket of moisture, dust, etc., in the atmosphere.

Effort test.—Persons who are clearly heat sensitized are usually sensitized to effort and vice versa. Indeed the excitant is probably the same in both cases, the heat being applied from the outside in one, and manufactured physiologically in the other.

There are many ways in which the effort test may be applied. Those used in the determination of circulatory function are appropriate. These are climbing a particular flight of stairs, hopping fifty times on one foot, raising dumbbells repeatedly above the head, or squatting on the heels a certain number of times. Each examiner must develop his own standards. Those which would be appropriate at sea level would be inappropriate at a high altitude, especially for persons recently arrived from low altitudes, who had not yet become acclimated. A test which would be appropriate for a mill worker would be too strenuous for one of sedentary habits. The procedure must therefore often be varied with the individual under observation.

As we have seen in the discussion of the mechanism of the allergic response, physical allergy is a phenomenon in which the gradations from normalcy through hyperergy, to allergy, may be most clearly followed. The patient with effort syndrome is hyperergic rather than allergic. He responds with tachycardia, dyspnea, fatigue, vertigo, and even syncope, to a quantum, or we might say dose, of effort which would not produce these same symptoms in the so-called normal person. The normal would, however, respond with these *same* symptoms if the effort were greatly increased. A hyperergic effort syndrome patient responds in a normal manner, but to what should have been an ineffective dose. If, on the other hand, the same relatively small dose results in true asthma or other truly allergic manifestation, one must recognize an allergy to effort.

In the study of physical allergy it is therefore desirable not only to recognize the allergic but also the hyperergic and any gradations between the two. Therefore tests which have been found effective in the study of effort syndrome should be particularly appropriate in the study of effort allergy. Since one should actually test for both conditions, one should study not only the allergic response but also the circulatory response. If we select the effort of hopping rapidly fifty times in succession as the average standard test, the procedure should be as follows. The patient is first examined for any allergic manifestation of the moment, and his pulse and respiration are determined, either sitting or, better, recumbent. He then undertakes the effort, following which the pulse rate and respiration are determined at one minute intervals, the patient being again either seated or recumbent. During this time and after, further search is made for any new allergic symptoms.

The average person in reasonably good physical condition will manifest a return to normal pulse rate and respiration within at most two minutes from completion of the effort. A delayed return may be taken as indicative of effort syndrome.

Discussion.—As with atopic and contact allergy there are all gradations in the intensity of the sensitization. When one is very mildly sensitized to heat, cold, effort or the actinic ray, prolonged exposure to the excitant, beyond that used in routine testing, might cause allergic manifestation. There-

fore in case of doubt, testing in any of these fields should be extended. The procedures described will, however, usually bring to light any reactions strong enough to be of clinical significance. At the other extreme, one may be so highly sensitized to any of these physical excitants that the routine procedure might produce severe reaction. Obviously, when the reaction has been definitely established, the test should be discontinued and, if necessary, corrective measures applied. As with heat allergy, the application of cold may be used to control the allergic response to effort.

Trauma test.—This is probably the earliest described manifestation of physical allergy although, naturally, it has not been designated as such until recently. Its commonest manifestation is that of dermatographia, the urticarial response to simple mechanical skin irritation. That it should be considered in this same class is brought out by Duke's observation that local areas may be temporarily exhausted or desensitized by repeated slight traumatization and that one may become acclimated by repeated mechanical irritation such as stroking the skin several times daily with a stiff hair brush, following which the intensity of the reaction remains greatly diminished.

Hot and cold air.—Physical factors applied to the mucous surfaces may also cause symptoms. This is seen especially in asthmatics after exposure to a wind, especially a cold wind, or when breathing cool air or air which is warmer than that to which the body is being exposed. Tests for this type of allergy are not required frequently since the patient's own description of his experiences usually gives the same information.

Testing with hot air may be done with a motor blower containing a heating coil such as an electric hair dryer. Testing with chilled air may be done through the delivery tube of a motor driven ice cooled oxygen tent. If the latter is not readily available, an air chilling device may be rigged up with a tin or galvanized box of about one cubic foot capacity. A circular opening about one inch in diameter is cut in one side, almost at the top. A similar opening is cut in the opposite side, the lower edge of which is about one inch from the bottom. The tank is filled to within one or two inches of the top with crushed ice, each piece being roughly the size of an egg. A one inch rubber hose is inserted about two inches into the upper hole. The motor blower is attached to this.

Air enters the lower opening, passes across the surface of the ice, out through the upper tubing and is delivered, chilled, from the motor blower. If no motor blower is available but compressed air is at hand, this may be forced in under light pressure at the lower hole and delivered in a steady stream through the upper tubing. In either method the patient holds the delivery tube near the mouth, breathing the warmed or chilled air.

The space in the ice tower below the lower opening serves as a water trap. Accumulated water may be poured out through the lower opening.

Obviously the ice tower will be more efficient if it is long and narrow rather than cuboidal, since the farther the two holes are separated the greater will be the exposure of the air to the surface of the ice.

Another method of applying cold air, not as efficacious but fairly satisfactory, is to place the intake tubing attached to a motor blower inside an electric refrigerator near the coil. The door is closed as far as possible and the crack reasonably well closed with towels or other available material.

A fairly efficient hot air blast may be rigged up using products from the ten-cent store. This consists of a six foot long wooden tunnel of approximately

four by six inches inside dimensions in which carbon filament light bulbs or bathroom heater units are set up in parallel. The intake end is connected with a compressed air supply, a motor blower, or an ordinary small electric fan.

Observations During Tests

We have mentioned that in the study of effort syndrome and effort allergy one should study the pulse and respiration. The blood pressure might also be followed, especially since there is a blood pressure response in cold allergies. Blood pressure and a record of the pulse and respiration might therefore be included in tests for all forms of physical allergy.

In addition, in our experience various shock tissues may react even though they are not the site of major interest to the patient. In testing for physical allergy in a case of urticaria one may observe pallor and edema of the nasal mucosa following the test even though the patient does not usually have symptoms of nasal allergy. For this reason the skin and nasal mucosa should be studied before, during and after the test, no matter what the major symptom. Sneezing is a response which should be recorded. Cough and wheezing should be recorded. The latter should be sought by pulmonary auscultation. Vital capacity determinations, before and after, may help. Observation should be made for possible delayed reactions such as urticaria and migraine. Diarrhea likewise may follow.

It is often difficult to correlate these delayed reactions with the tests since other intervening factors might be playing a part. For this reason it is sometimes necessary to repeat the tests at intervals.

Discussion

We have seen that Bostock who in 1819 first described hay fever, took vigorous exception to Elliotson's suggestion that pollen might be the etiologic agent. Duke points out that Bostock may have been correct in his own case since he may well have been a physical allergic. Bostock suffered from "summer catarrh" which he attributed to the effect of heat and the sun's rays. He learned that by the avoidance of exertion and moist close atmospheres and with an abundance of fresh air he could relieve his symptoms in some measure. Fresh air presumably laden with pollen produced relief rather than exacerbation.

Types of response. Duke divides the response to tests into two types, "contact reactions" and "reflex-like reactions." The former occur at the site of contact with the excitant while the latter may develop in remote tissues or become generalized. The former are more easily identified. In the cold test the subsequent edema of the hand is a contact reaction, while urticaria, nasal reaction or constitutional reaction would be "reflex."

The contact reaction is remarkably similar to that observed in atopic patients. Duke states that the family history is the same in each type and that local reactions are similar except that contact reactions are not accompanied by pseudopod formation. This is probably due to the fact that in testing with atopic allergens, the excitant spreads through the lymph channels. Duke observed eosinophilia, local exhaustion of reaction capacity, local tolerance following repeated exposure, constitutional reactions if the dose is sufficient, and a normal response to epinephrine, with improvement but not complete cessation of the reaction.

In the reflex-like or systemic reaction Duke finds that heat or cold may cause orbital or nasal symptoms, reactions involving the bronchi, the skin

erythema, pruritis, urticaria, angioneurotic edema), or the gastrointestinal tract (severe abdominal pain following the ingestion of cold drinks or food and diarrhea following the ingestion of hot drinks or food). Heat or cold may cause shock. Actinic rays entering the eyes, as by looking at the sun, may cause orbital and nasal reactions. Sneezing is the commonest of the latter.

He finds that, except for the effect of light upon the retina, reflex-like reactions are due to heat or cold. This includes effort. He finds heat sensitiveness more common than cold sensitiveness.

Duke, likewise Harris, Lewis and Vaughan suggest that "chilblains" may be due to cold allergy. This is a local edema, usually of the feet or hands, with considerable pain, following exposure to cold. Once a person has developed chilblains, he does so thereafter following much less intense cold exposure than formerly. It is a question whether this should be termed allergy or hyperergy.

Deaths from drowning.—The reflex-like constitutional reaction following exposure to cold may be so severe as to cause syncope. Horton, Brown and Roth suggested that this may be a factor in the drowning of good swimmers. Among 22 subjects 14 had systemic reactions, 11 with syncope. In 9 the syncope had occurred after swimming and 4 of the 9 had been rescued from the water. From the literature Horton et al. gathered records of 76 cases of cold allergy not including their own. Of these, 29 had had constitutional reactions, 18 with syncope. In 15 of these the syncope had occurred following swimming. Four had had to be rescued from the water. Altogether this amounts to 24 cases of syncope following swimming.

The writer has observed a case of syncope following swimming, in a person who did not react to cold but to heat and effort. The heat and effort of swimming appeared to be responsible for the syncope.

One of the earliest cases of cold allergy described was that of Behier (1866) who customarily developed urticaria after swimming and who found that too long exposure in cold water produced syncope.

Complicated types of response.—The difficulty of recognizing physical allergy when the symptoms are indirect or remote or, as Duke expresses it, reflex-like, is further increased by the fact that a combination of two or more physical agents such as heat or cold may produce symptoms while neither alone will. Thus, a cold wind may not produce symptoms following inhalation or contact with the respiratory mucosa unless at the same time the skin surface is heated. Routine testing as described is usually applied to the skin. Yet Duke states that the respiratory mucosa is more frequently sensitized than is the skin. In this type it is sometimes advisable to employ the inhalation test with heated and chilled air.

Eczema of exposed areas should make one suspicious of light or cold allergy. If shaded areas of the skin such as the forehead are relatively unaffected, light especially should be under suspicion.

Some persons react to heat only if exposed to cold just prior to the heat exposure and vice versa. This is the reason for Duke's procedure of repeating the heat and cold tests alternately in case of doubt. The sensitization appears to be not so much to the actual temperature but to the change of temperature. In such cases the patient often finds difficulty in correctly recognizing the offending agent. Duke describes a case with a history of having urticaria each year during the first cold days of autumn, attributed by the patient to chilling. He found that the patient reacted only to heat, and only to heat following prolonged exposure to cold. Therefore he had heat symptoms only during cold weather.

Again, a woman had asthma only following exposure to cold. When tested with ice rubs and refrigerated air she did not experience asthma but when subsequently exposed to normal or warm temperatures an asthmatic attack immediately supervened.

Another of Duke's interesting cases is one of nasal allergy due to heat. The inhalation of warm air did not produce symptoms as effectively as when this was combined with the application of ice to the skin of the body. The condition was relieved by the application of ice compresses upon the nose. This latter procedure was more effective if the rest of the body was heated at the same time.

A patient allergic to cold had a few hives. Ice rubs did not increase their number. General application of heat caused disappearance of the hives. Immediately following this the reapplication of ice resulted in a severe general outbreak of hives, much more than ice had caused when not preceded by heat.

Sometimes exposure must be prolonged. One of Duke's patients with urticaria and angioneurotic edema, allergic to heat, found it necessary to stay in a hot bath at least thirty minutes before the symptom supervened.

Insofar as possible the conditions of the test experiment should reproduce the conditions which normally cause symptoms. If a person experiences asthma following exercise, only in cold weather, the test should be made with the inhalation of cold air while heat is being applied to the skin or the patient is exercising.

Duke states that the heat allergic is likely to react most markedly when the body temperature is subnormal. The heat allergic may therefore react mostly during the winter months or on cold nights. Many heat allergies are symptom free in warm weather. They are likely to be at their worst after midnight when the temperature of the air and the body temperature are low. They may be entirely symptom free at other times during the day. A temperature chart record for several days during the period of symptoms may give a lead, since the heat allergic is sometimes inclined to react only when his temperature is subnormal. The heat allergic may find himself free from symptoms for quite a time following an acute febrile attack.

Passive transfer.—The term atopy is limited to those allergic manifestations in which reagins are shown to exist and in which passive transfer may be accomplished.

Duke was unable to demonstrate the transfer of allergy to trauma. One thousand cc. of blood from a dermatographic donor was transfused into a patient with pernicious anemia. The recipient did not become dermatographic. Serum from a patient allergic to cold was transferred into the skin of several pollen allergies. The latter did not become locally cold sensitized.

A. Walzer did succeed in transferring urticaria factita to normal skin in one of twelve cases. Even in this one case not all passive transfer recipients reacted.

Harris, Lewis, and Vaughan did transfer sensitization to cold. Apparently passive transfer is a possibility which is, however, rarely accomplished.

H-substance.—Sir Thomas Lewis in the development of his theory of the *H-substance* did much of his work with physical allergy, especially dermatographia. In 1927 Harris showed the existence of a substance in the skin which produces a histamin-like action on the guinea pig uterus, with resulting smooth muscle contraction. The epidermal layers were more active than the deeper tissues. This is consistent with other observations that histamin is especially abundant in the tissues of the skin, the lungs, the liver and the intestines.

Lewis postulated local liberation of the histamin-like substance. Gastroenterologists have demonstrated that the injection of histamin will increase gastric acidity. Kalk demonstrated that irritation of the skin of a dermatographic patient by means of a brush caused an increased gastric secretion and acidity. Horton, Brown, and Roth showed the same true in persons allergic to cold during and following cold tests.

These observations give further corroboration to the theory of Lewis on the liberation of the histamin-like substance.

Therapeutic importance.—The recognition of physical allergy is important, since Duke and others have shown, and we have found in our own experience, that treatment is usually efficacious. The acute attack can usually be relieved by the application of the opposite factor and tolerance to the exciting agent can usually be increased by repeated small exposures. Duke gives an unusual example, a cold asthmatic, relieved following exercise (internal heat). Here was an asthmatic who, according to custom, should not be made to exercise on account of his asthma, but who found that exertion relieved symptoms.

Horton, Brown, and Roth find that cold allergy may be relieved in a few weeks by having the patient dip his hand into cold water for six minutes twice daily as in the test. They find also that daily immersion of the hand in water, starting at 65° F. and gradually decreasing the temperature as tolerance is acquired, to 45° or thereabouts, gives relief. They find that 0.1 mg. histamin twice daily gives relief. I have observed that in patients reactive to heat and effort a similar procedure with the immersion of the hand in warm water twice daily, the temperature of which is gradually increased from 98° to a top of about 108° or 110°, accomplishes the same results. After the patient tolerates hand immersion at 108° he commences tub baths at about 100 degrees with steady increases thereafter. In an unusually highly sensitized patient reacting both to heat and effort, the writer found that after the patient had reached a stage at which she could tolerate a tub bath at 108°, further treatment with calisthenic exercises relieved her of all symptoms. The total time required was about six weeks.

Physical allergy in atopic persons.—Duke believed at first that physical allergy and atopic allergy do not usually occur in the same person. Swineford found that physical allergy is not at all uncommon among atopic allergies. My own experience confirms this conclusion.

Swineford found that in 325 allergies physical allergy was an excitant for the chief complaint in 95 and served as an aggravating cause in 106. In only 3 was physical allergy deemed the chief excitant. In 99 it was a major factor although atops were of equal importance. In an additional 99 it served as an excitant of minor importance which, however, colored the picture. Even in migraine physical allergy was found to be a factor of major importance in 15 of 26 cases.

Like Swineford, we find tests for physical allergy to be an important adjunct in the routine testing of all allergies, atopic and otherwise. When physical reactions are taken into consideration, even as minor factors and are adequately controlled, therapeutic results are better.

Other Observations

Henry (1930) described a man allergic to heat and effort who could produce urticaria at will by bending forward and touching the floor with his hands six times in succession. Cool water relieved the symptom. He described a person apparently allergic to both heat and

cold. Either test reacted positively. Following effort such as tennis he reacted with urticaria, generalized edema, loss of voice and vertigo. This could not be relieved by a cold shower.

Morey and Mitchie (1930) described sensitization to heat and effort. 80 per cent temporary relief followed daily histamine injections.

Alexander (1931) reported the case of a woman allergic to heat who, following experimental exposure under a warm shower for five minutes, developed an intense urticarial eruption, vertigo, and nausea. Daily shower baths with gradual increase in the temperature of the water and lengthening of exposure relieved the symptoms.

Wilson (1931) described heat allergy in a man who first noticed urticaria developing at his belt line. Living in Iowa he found it necessary to work in his shirt sleeves in the winter time to keep cool. He was able to do little or no work in the summer. He moved to Tucson, Arizona where his symptoms were worse. The interesting feature is that the administration of thyroid extract completely and apparently permanently relieved the symptom.

Weiss (1932) under the title *urticaria solaris* reported two cases of actinic allergy and reviewed the literature on the subject. The first was a man who for seven years had experienced swelling and itching of the face and neck, always worse in summer. Standing bare-headed in the sun for two hours produced symptoms. Once while driving without a coat and with his shirt sleeves rolled up, the exposed left arm reacted with angioneurotic edema. This patient had subconsciously always selected the shady side of the street.

Other actinic cases have been described by Ward (1905) and Ochs (1910). Some patients react to the visible light spectrum rather than infrared or ultraviolet.

Bray (1932) discussed a case of cold allergy. Ten minutes' exposure of the hand in cold water produced chilblain. The skin appeared to be the shock tissue involved since the mucous membranes were unresponsive, no reactions following the sucking of ice. Cooling of the skin with ethyl chloride spray produced positive response. The application of a tourniquet above the immersed hand prevented systemic response. Four per cent eosinophiles were found in the immersed hand as contrasted with none in the other hand and 2 per cent in blood obtained from each hand prior to the test.

Bray "desensitized" with subcutaneous daily injections of histamine commencing with 0.1 mg. and increasing to 1 mg. The two final doses were repeated on several days with a total dose of 16.2 mg. (25 injections) over 27 days. Histamine injections were followed within two minutes by flushing from peripheral dilatation and, when pronounced, shivering and faintness. A wheal developed at the site of injection. Blood pressure fell. Often there was an associated severe headache. All symptoms passed off within twenty minutes. Following histamine treatment and continued cold therapy the patient remained relieved after approximately two months.

Bray remarks that patients allergic to one physical agent rarely react to another.

He found 26 reports on idiosyncrasy to cold up to 1932. Where sex was indicated, 16 were male, 18 female. The youngest male was 15 years, the youngest female 11. The oldest male was 64, the oldest female 57.

He points out that the cold allergic is very active, in contrast to the heat allergic who generally seeks a life of tranquillity. In the former, especially, the temperature charts are subnormal and irregular. Reactions are inhibited during fever and following exercise and are exaggerated when the temperature is subnormal.

Swineford and Weinberg (1933) report a case of extreme allergy to heat. A woman aged 43 had had severe asthma of three years' duration. She also had sinus infection. Within thirty seconds of exposure of the chest to an infrared lamp she developed asthma. Ice rub gave beginning relief in one minute, complete in four minutes. During reaction râles appeared, which cleared with recovery. A hot water bag applied to the chest produced similar response. The same occurred after exposure of the chest to the heat of a 40 watt electric bulb, one foot away. Even the heat of a towel placed over the face caused asthma. This patient was relieved following intravenous typhoid vaccine injections.

Bray (1935) described cold allergy in a seven-year-old child in whom local eosinophilia was observed at the site of reaction.

Kobacker and Parkhurst (1935) report the development of cold allergy in three sisters, following an attack of measles.

Other writers have been Hopkins and Kesten (1934), Hill and Clement, Mollison (1929), Covisa and Prieto (1930), Spiesman (1933), and Peters and Hoffman (1934).

Saylor and Wright (1936) have made a very complete study of a cold allergic who experienced local and systemic reactions (throbbing headache and generalized flushing) after

exposure of a skin area to cold air or cold objects. Ice cream or chilled food caused her throat to swell and interfered with swallowing. Exposure to cold air caused her face to swell. A similar local reaction would follow the carrying of a cold milk bottle. Symptoms first became manifest after local infection in a finger. In the beginning the local reaction, edema, would occur only in this finger. Later the symptoms were more generally distributed.

Exposure for an hour in a room at 22.3° C. caused no symptoms. However, contact with a metal cabinet, the temperature of which was 1.2 degrees higher than that of the room, produced symptoms. The room did not seem cold but the cabinet did. The metal removed heat from the arm more rapidly than did the air. Actually the arm became cooler more rapidly with this latter form of exposure. Four minutes' contact sufficed to produce local reaction.

These authors found that the local reaction to cold, after removal of the excitant, was accompanied by an increase in temperature. Contrary to the observations of Bray and Levine they found no local eosinophilia. Like Horton and Brown they did observe an increase in gastric acidity, suggesting a histamine-like effect.

The application of 10 per cent menthol in alcohol to an area of the skin is said to produce the same reaction as cold in cold allergies. Saylor and Wright did not find it true in their case. Anesthetization of an area of the skin with 2 per cent novocaine removed all sensation of cold during the test but the local reaction with edema supervened nonetheless. It was not as marked. Passive transfer tests were negative. They found that edema fluid obtained from the area of local reaction, when injected into an uninvolved area, caused wheal formation.

This patient was not found sensitized to atopic reagents. Treatment with histamine hydrochloride 1:1,000 beginning with 0.1 cc. and increasing to 0.5 cc., after which this latter dose was given subcutaneously three times weekly, eventuated in 60 per cent relief. Whereas preceding treatment the patient was unable to leave the house when the temperature was below freezing, during the winter in which she was receiving treatment she was able to go out in temperature as low as 10° F. without severe symptoms.

Duke (1932) has described cases with angina pectoris, tachycardia (rate 160 to 180) and ventricular extrasystoles in which the symptoms could be initiated by heat, cold or effort and terminated by the application of the opposite agent.

Summary

From a review of the above literature we must conclude that the concept of physical allergy as developed by Duke has been substantiated by the observations of a number of investigators. Contrary to Duke's experience, I have yet to see a case of pure physical allergy in which no atopic allergy whatsoever can be demonstrated. There is, however, no reason why this should not be the case, and the experiences reviewed above would indicate that it often is. But, even in the atopic allergies physical allergy may play a role of major importance or may be a minor or conditioning factor which should be taken into consideration and appropriately treated if one would obtain best therapeutic results.

CHAPTER XXVI

THE DETERMINATION OF VITAL CAPACITY

BY DR. JAMES HOLMAN

Definitions.—Normally we breathe in or out about 500 cc. of air. This is the *tidal air*. It is much less than we are capable of breathing with maximum effort. If at the end of ordinary inspiration one endeavors to fill his lungs to full capacity, one will draw in an additional 1,500 to 2,000 cc. The additional volume is *complemental air*. If at the end of ordinary expiration one continues to expire until no more air can be expelled, an additional 1,500 cc. may be breathed out. This is *supplemental air*. The entire range between maximum inspiration and maximum expiration is termed the *vital capacity*. This includes tidal air, complemental and supplemental air. While, as stated, normal respiration involves the exhalation or inhalation of only about 500 cc., the maximal amount or vital capacity involves 3,500 to 4,000 cc.

Even after maximal expiration, there is still air in the lungs. This is the *residual air* and in an adult normally amounts to about 1,500 cc. Residual air is divided into two moieties, *alveolar air*, that remaining in the alveoli, and the *dead space air*, that in the air passages not including alveoli. The latter comprises 150 to 250 cc. of the residual air.

Variation in vital capacity.—Vital capacity is surprisingly constant among normal persons of similar build. Obviously there is some variation depending upon sex and muscular development, but these factors are taken into consideration in the calculation of what should be the normal vital capacity for a given individual.

Pulmonary disease usually diminishes vital capacity. This is observed in tuberculosis, asthma and cardiac disease with pulmonary congestion.

The vital capacity is markedly reduced in severe asthma, moderately in mild asthma, and may be normal in asthmatic patients who are not suffering from asthma at the time of testing. Serial determinations of the vital capacity are of value in establishing evidence of improvement during therapy.

Technic.—Any simple spirometer of from six to eight liters' capacity should be satisfactory. In its simplest form this consists of an inverted cylindrical bell, properly counterbalanced, sealed with water, into which air may be blown from below. Such an outfit is available in the basal metabolism apparatus. At least one of the standard metabolism testing outfits provides the necessary additional equipment for determination of vital capacity. This consists of a mouth piece attachment, a ruler for measuring in liters the amount of air exhaled into the spirometer, and tables for calculation of the normal vital capacity based upon sex, age, height and weight.

The test is performed with the patient standing, thereby facilitating maximal inspiration. He inhales as deeply as possible, then blows as much air as possible through the mouth piece into the spirometer. The air delivered is measured in liters or cubic inches, preferably the former. At least three such expirations are performed. Patients, especially children, not previously acquainted with the procedure, must sometimes repeat the process a number of times. Final determination is based on the maximum expiration rather than the average. In following progress in the treatment of an asthmatic the vital

capacity need not necessarily be compared with the normal for sex, age, height and weight, since the first determination prior to treatment will serve as a standard for future comparisons. However, it is desirable to know at the beginning whether the vital capacity is normal or reduced. For this reason, the percentage of normal should be ascertained.

Normal standards.—West has found that vital capacity varies more with the surface area of the skin than with factors such as standing-height, sitting-height, weight. West's standard is determined by dividing the vital capacity by surface area. The height and weight being known, surface area is determined by reference to surface area charts as used in basal metabolism determinations.

He finds the normal vital capacity for men, 2.5 liters per square meter body surface, that for women 2 liters.

Pratt has found that age factors play a distinct part. Vital capacity attains its maximum in the third decade, after which it slowly decreases. It is lower in women than in men of the same height and age. He finds the variation from West's standards in men at various ages as shown in Table XXI.

TABLE XXI. VITAL CAPACITY AND AGE

AGE	AVERAGE PER CENT OF WEST'S STANDARD
10-20	82
20-30	105
30-40	90
40-50	83
50-60	83
60-70	73
70-80	56

Ten or at most 15 per cent variation from the normal standard, age considered, is within the normal range. The physical condition of the subject also plays a part. Dreyer grouped his subjects in accordance with the mode of life, into (a) the athletic type, (b) the professional and business type and (c) the sedentary type. Class *b* has a vital capacity about 9 per cent under that of Class *a* while Class *c* is about 15 per cent under Class *a*. A vital capacity more than 15 per cent under the normal should be classed as definitely reduced. From 10 to 15 per cent is probably somewhat reduced.

The vital capacity of an obese person is not as great as that of a nonobese of the same height and weight.

There can be no entirely set standard for height and weight or surface area in determination of vital capacity since several factors tend to affect it in persons in good health. These include excessive physical training and certain occupations which may overdevelop vital capacity. Other occupations may retard its development. At about the age of 45 a gradual reduction in vital capacity commences which becomes more pronounced with increasing age. Obese persons do not maintain the usual correlation with weight or surface area. With them the correlation is best obtained by comparison with the height.

Myers states that in the recumbent position the vital capacity is about 5 per cent lower than when erect. Race and nationality play a part. The vital capacity in the female is so much lower than in the male that two separate standards are required.

For children Edwards and Wilson find a better correlation between vital capacity and height than between vital capacity and surface area or weight.

They find on an average 15.5 cc. vital capacity for each centimeter standing weight.

Myers states that more accurate vital capacity determinations may be obtained with emaciated patients when the patient's usual weight or theoretical normal weight is used in the calculation rather than his actual weight. In both emaciated and obese cases the standing-height standard may give better results than surface area or weight. When recording the vital capacity, the type of standard used should be indicated.

Charts for evaluating vital capacity. Edwards and Wilson have devised a chart from which, given the surface area and measured vital capacity, the

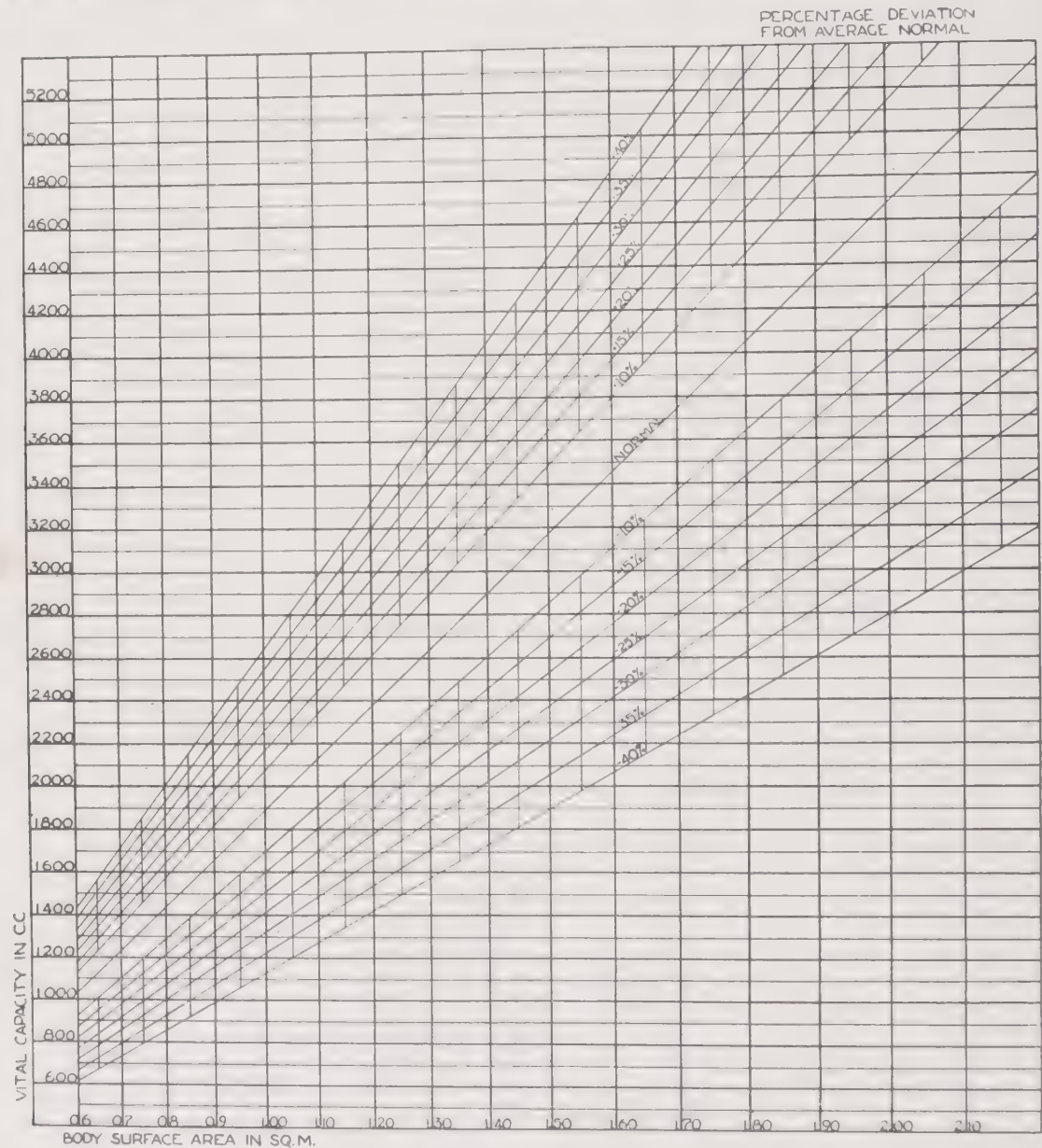


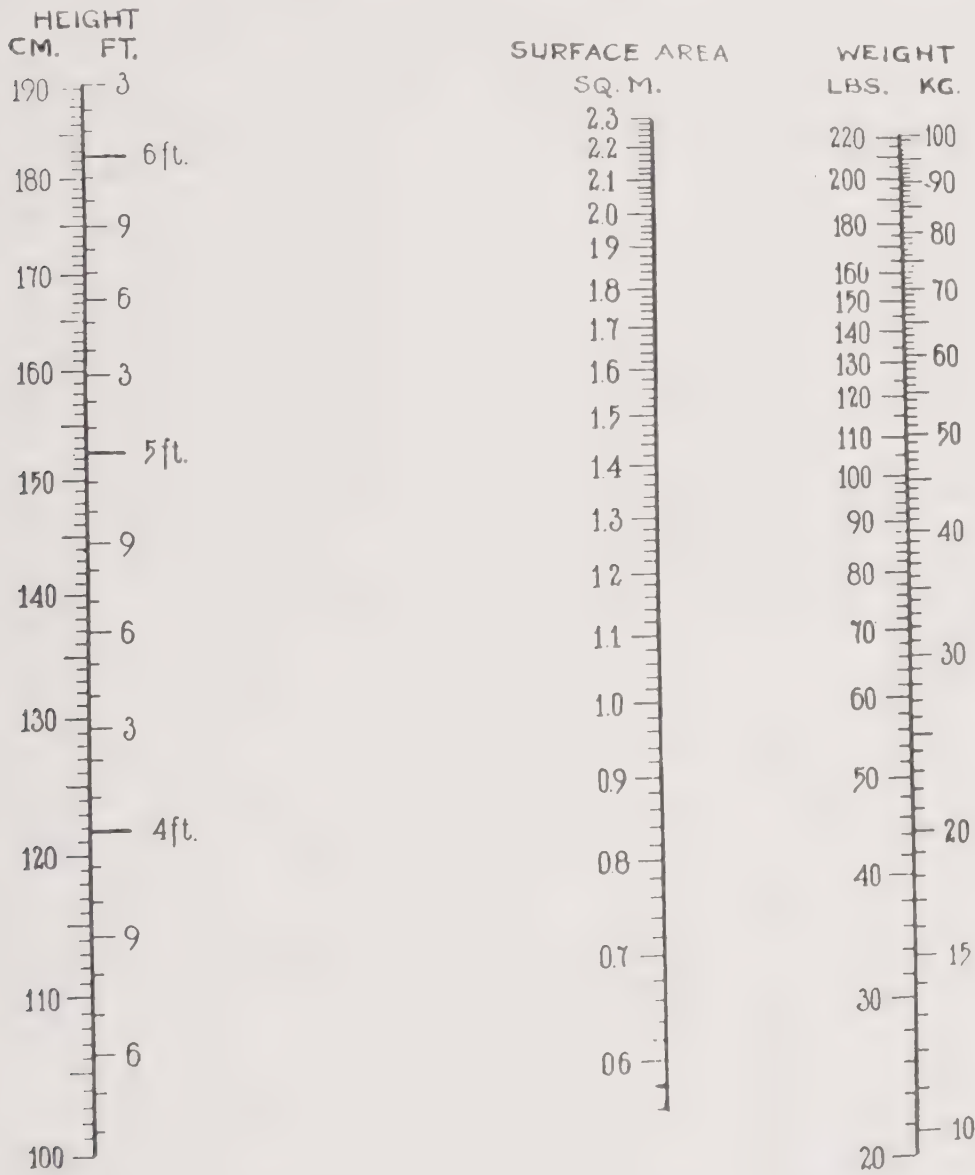
CHART FOR EVALUATING VITAL CAPACITY MEASUREMENTS

Fig. 51.—Vital capacity determination. Per cent above or below normal is read at the intersection of the horizontal line for recorded vital capacity and the vertical line for surface area. (Charts included through the courtesy of Doctors Dayton J. Edwards and May G. Wilson, J. Lab. & Clin. Med. 24: 543, 1939.)

increase or decrease from normal may be measured direct in percentage (Fig. 56). Surface area may be determined, height and weight being known, from the Du Bois Chart or the Boothby and Sandiford Chart, which are commonly used in basal metabolic rate determination.

Discussion

Although Borelli (1679) first attempted the measurement of the quantity of air that could be inhaled, it remained for Jonathan Hutchinson (1846) to invent the spirometer and apply its use in the study of disease states. He described the



NOMOGRAM FOR DERIVING
BODY SURFACE AREA

Fig. 52.--To determine surface area, place straight edge at patient's height and weight. The ruler cuts the central figure at the correct surface area. (Courtesy of Doctors Edwards and Wilson.)

vital capacity as the greatest voluntary expiration following the maximal inspiration. He believed that the vital capacity varied with height. "For every inch in height (from five feet to six feet) eight additional cubic inches of air at 60° F. are given out by a forced expiration." West has demonstrated the superiority of surface area over height in determining the value for normal vital capacity.

The efficacy of the test in clinical medicine is due to the fact that it is a relatively simple, nonexpensive test that gives an answer in terms of function. That the x-ray offers valuable aid in the diagnosis of chest diseases is unquestionable, however, the determination of the vital capacity affords rather accurate knowledge of functional ability in both reversible and irreversible pathologic conditions in the lungs.

Cardiac disease. Peabody (1917) and his collaborators have shown that vital capacity determinations are a valuable aid in following the progress of left ventricular heart failure. In severe heart failure the vital capacity drops to below 25 per cent of normal. Its return to normal is concomitant with the progression of the treatment. Serial determinations of vital capacity, therefore, offer a good index as to the progress of treatment of left ventricular heart failure.

Harrison (1936) has used this determination in studying dyspnea in cardiac patients. In those patients who experienced dyspnea on exertion, he devised a standard type of exercise for the patient to do for two minutes and then rest for five minutes. In those patients who were not neurotic, subjective respiratory distress appeared when the value of the ratio:

$$\frac{\text{Ventilation (for the 7 minute period)}}{\text{Vital Capacity}} \text{ was 25 to 30. This was true in both}$$

normal subjects and in the patients, although the latter, because of their lowered vital capacities, were usually dyspneic at a considerably lower ventilation than were the normals. He has also used the principle that dyspnea is related to the ratio:

$$\frac{\text{Ventilation in liters per minute (per square meter)}}{\text{Vital Capacity in liters (per square meter)}} \text{ in the study of patients with}$$

cardiac failure who experienced dyspnea at rest. Normal values for the resting ventilation are 1.2 to 1.4 for the basal states and 1.4 to 2.0, for the resting (but not basal) condition.

Bronchial asthma. Vital capacity determinations have a twofold purpose in studies of patients suffering with bronchial asthma. (A) As an index to the severity of the attack, as well as the value of therapeutic agents administered during the attacks. (B) When the patient is completely free of the acute attack, determinations help the physician to ascertain the amount of permanent pathological changes in the lung parenchyma.

(A) Many investigators including Peabody and Wentworth (1917), Myers and Cady (1925), Mudd (1925), and Lewis (1932) have reported that the vital capacity is reduced during the acute attack in children and adults, and returns to normal following the cessation of the attack. Feinberg (1930), in studying this problem in a group of 88 patients, found that in adults, the vital capacity did not return to normal between attacks. The average was 82.3 per cent. The children in his group showed 97.8 per cent normal vital capacity between attacks. Such complications as emphysema, chronic bronchitis, bronchiectasis, and cardiac disease could help explain this decrease in the vital capacity of the adults.

In general the reduction of the vital capacity in the acute attack is proportional to the severity of the attack. In very severe attacks it will fall below 20 per cent of normal. In these patients with severe asthma it is difficult, if not impossible, to get a true value because the patients are very fatigued from the dyspnea, and other factors as coughing, for example, interfere with the ability of the patient to carry out the test properly. In fact, one should not subject a patient who is experiencing violent dyspnea to this or any other procedure that will not help him gain relief.

(B) There are many complications of bronchial asthma. Emphysema is perhaps the most common and important. Alexander (1941) states, "As a result of prolonged obstruction from any cause, emphysema occurs. It is a constant complication of chronic asthma, and a serious one, for it interferes with pulmonary function. The alveolar walls stretch, thin out, and may rupture."

Perhaps it is not amiss to list some related experimental evidence. Printzmetal (1931) has showed in animal experiments that low oxygen tensions and also high carbon dioxide tensions in the inspired air would produce an increased negativity in the intrapleural pressure. Patients with bronchial asthma have some degree of anoxemia and carbon dioxide retention. In unpublished experiments of Holman and Shires on dogs anesthetized with sodium-pentobarbital, simultaneous recordings of intrapleural pressure and tidal exchange were made. Minute rate and ventilation were also obtained. The mean intrapleural pressure became more negative on the administration of pilocarpine. When the dosage was increased, the dogs then demonstrated very active expiratory effort and as a result the mean intrapleural pressure began to rise. There was marked fluctuation in the intrapleural pressure corresponding with the different phases of respiration; expiratory intrapleural pressure began to exceed atmospheric pressure; and, the minute ventilation dropped below normal. Printzmetal (1934) also has shown that the intrapleural pressure relationships in bronchial asthma are negative even at the end of expiration in moderately severe asthma. He further states that expiration does not become active until extreme dyspnea is experienced. To test the hypothesis that decreased intrapleural pressure might cause emphysema, he subjected rats to low atmospheric pressure (350 millimeters to 450 millimeters mercury) in special tanks. This corresponded to approximately 60 millimeters oxygen tension, resulting in a decrease in the mean intrapleural pressure. After a period of one to ten weeks the rats were removed and their lungs examined. The sections revealed thinning of the walls and coalescing of the alveoli. Campbell (1927) has reported similar experiments.

Sudsuki (1899), Nissen (1925), Kountz, Alexander, and Dowell (1929), and Loescheke (1928) have devised means of experimental air-way obstructions in animals that produced lesions indistinguishable from the variety of emphysema which follows bronchial asthma.

It is important to distinguish pulmonary distention from true emphysema. The former indicates increased air in the lungs with retention of elasticity, whereas in the latter there is an increased amount of air in the lungs, associated with a loss of elasticity. The intrapleural pressure hovers about atmospheric pressure rather than an increased negativity as seen in pulmonary distention.

Vital capacity determination offers a good method of objective measurement of the progress of a chronic disease such as asthma which often leads to irreversible pathologic changes. An important problem arises in patients seen for the first time who have the physical signs associated with emphysema but are wheezing mildly at the time, as to how much of their history of dyspnea is due to the asthma, which under proper therapy is reversible, and how much is due to ir-

reversible pathologic changes. Vital capacity determination made before and following any therapeutic procedure, that will alleviate the active asthma, will help elucidate this vital and important question. It is not uncommon to see a patient in the second and third decades of life with a history of asthma since early childhood, with an emphysematous type of thoracic cage, have a normal or near normal vital capacity. Contrasted with this is the patient, usually seen in later life with a short history of asthma, an emphysematous type of thoracic cage, having a marked reduction in vital capacity indicative of a reduced functional ability to ventilate properly. The former type patient has pulmonary distention and probably some beginning emphysema, whereas the latter has true emphysema with the loss of elastic tissue and other changes characterized by this entity.

Emphysema.—Alexander found that pulmonary emphysema very materially reduced the vital capacity, the latter being restricted proportionately to the increase in residual air. In advanced emphysema the vital capacity may be reduced as much as 75 per cent. Such a reduction prohibits even mild exertion.

He found vital capacity much more reduced in obstructive emphysema such as accompanying asthma (average 55 per cent of normal) than in the nonobstructive or senile emphysema (average 85 per cent normal). In the latter the diaphragm still functions, emphysema being due to arthritic changes in which the vertical length of the spine is reduced by thinning of the intervertebral discs. Approximation of the vertebrae raises the anterior end of the ribs and sternum. Respiration becomes more predominantly diaphragmatic. The chest becomes barrel shaped. In the obstructive emphysema of asthma, on the other hand, the ribs are maintained in the inspiratory position and the diaphragm pressed downward. It is relatively immobile. These facts account for the difference in vital capacity in nonobstructive and obstructive emphysema.

Effect of Epinephrine, Ephedrine, and Theophylline Ethylenediamine

(A) Bronchial asthma.—The rapid amelioration of symptoms following epinephrine and related drugs would lead one to anticipate that this therapeutic procedure would lead to an increase in vital capacity. Mudd (1925) studied three asthmatics during an attack with vital capacities of 1,508 cc., 1,182 cc., and 790 cc. Following the administration of epinephrine they showed an increase in capacity of 71 per cent, 20 per cent, and 100 per cent, respectively. Colmes, Medalia, and Factoroff observed twenty-seven patients, and reported that although relief was prompt following the administration of epinephrine, the improvement in vital capacity by no means paralleled the symptomatic response. One patient, for example, had a normal vital capacity of 4.4 liters. During an asthmatic attack it was reduced to 3.3 liters. Epinephrine gave prompt relief and increased the vital capacity to 3.8 liters. In this group epinephrine had no effect on vital capacity in two cases, while in three cases it was actually reduced by from 2 to 12 per cent. In the remainder the capacity was increased from 1 to 25 per cent. "What impressed us most in these observations is the fact that all patients felt relief from dyspnea after they received a dose of adrenalin, notwithstanding the fact that the change in vital capacity was not always in their favor. . . ."

In a group of ten patients admitted to Parkland Hospital for study during numerous attacks of moderately severe asthma over a period of one year, vital capacity determinations were made before and after the administration of three drugs: theophylline ethylenediamine injected intravenously in dosage of 500 mg., epinephrine 0.5 mg. given intramuscularly, and ephedrine 45 mg. given intramuscularly. The vital capacities of these patients ranged from 18 to 50 per

cent normal. The results of these studies indicated that the efficacy of the drugs as therapeutic agents in the treatment of the acute attack of asthma both subjectively and objectively (as measured by increase in vital capacity) were respectively theophylline ethylenediamine, epinephrine, and ephedrine. At no time did any patient demonstrate over 1,000 cc. increase in vital capacity. On several occasions a patient would experience some relief from his dyspnea and yet show a slight decrease in vital capacity. This phenomenon was explained, to our satisfaction, as due to the fact that the patient would not expend his maximal effort, usually because of the tendency to make him cough. In general, with these exceptions, the increase in vital capacity paralleled fairly closely the subjective improvement.

(B) Emphysema.—Alexander found that in obstructive emphysema 1:1,000 epinephrine 0.5 cc. caused an increase in vital capacity within five minutes. The average increase was 350 cc. Those with obstructive emphysema due to asthma did not do as well as those with obstructive emphysema due to chronic bronchitis. He attributed this to the difficulty in expelling the thick tenacious mucus. Ephedrine also produced good results and this was preferred because it could be used more continuously.

(C) Cardiac asthma.—Harrison (1936) and Heyer (1946) studied the effect of theophylline on patients with congestive heart failure with and without sibilant rales over the entire lung field. Four of the five patients, studied by Heyer, had vital capacities slightly under 50 per cent normal and one had a capacity of 79 per cent normal. These patients showed an increase in vital capacity following 500 mg. theophylline ethylenediamine intravenously ranging from 150 cc. to 800 cc. This increase compared favorably with the increase seen in many patients with bronchial asthma.

Relationship of Arterial Blood Oxygenation to Vital Capacity

(A) Bronchial asthma.—Meakins studied five patients during acute attacks of asthma. These patients had varying degrees of bronchitis and emphysema. The arterial oxygen saturations varied from 85 per cent to 91 per cent. "On analyzing these cases of chronic bronchitis and emphysema, and asthma where pathological conditions occur in varying degrees of prominence, it is found that there is consistent lowering of the arterial blood oxygen saturation percentage. In a rough way the lowering of the arterial blood oxygen saturation is directly proportional to the chronicity of the lesion or, in other words, to the extent of the emphysema and chronic bronchitis." Unfortunately, vital capacity determinations were not recorded in this series. Holman and Shires studied a group of asthmatics and found the same correlation as did Meakins. For example, one patient (without chronic emphysema) with a vital capacity of 30 per cent normal during a moderately severe acute attack of asthma had an arterial blood oxygen saturation of 93.1 per cent. Another patient with marked emphysema associated with long standing asthma had an arterial blood saturation of 85 per cent during an attack of asthma. His vital capacity was 30 per cent normal. It is obvious, however, that a patient might not have any signs of chronic emphysema and have a severe enough attack of asthma to have a markedly lowered arterial blood oxygenation.

(B) Cardiac decompensation. Numerous investigators have reported various degrees of arterial blood oxygen unsaturation in cardiac decompensation. Harrop found that in most of the cases in his group, during the state of decompensation, the oxygen saturation of the arterial blood was reduced from normal 95 per cent to 80-90 per cent. The cause of the arterial anoxemia, as pointed out

by Harrop, is the abnormal condition of the lungs which are edematous because of pulmonary stasis and various degrees of emphysema which are frequently associated with congestive failure. However, not all patients have reduced oxygenation of the arterial blood. Harrison, in his book, *Failure of the Circulation*, has recorded numerous studies of arterial blood gases in patients with pulmonary congestion, pulmonary edema, and cardiac asthma. Pulmonary edema causes a marked reduction in oxygenation. One of his patients, during an attack of pulmonary edema, had an oxygen saturation of 56.4 per cent. Vital capacity was not recorded on this patient. However, in three other patients with cardiac asthma, his studies indicate oxygenation of 100 per cent, 92.8 per cent, and 92.4 per cent. The vital capacities of these patients were respectively 2.04, 2.49, 2.24 liters. It is quite evident from his studies that fluid in the air passages reduces the oxygenation markedly, but that the arterial blood may be completely saturated during pulmonary congestion despite a marked reduction of vital capacity.

(C) Emphysema.—Scott (1920), Meakins and Davies (1920), and Christie (1934) have reported cases of pulmonary emphysema associated with some degree of arterial blood oxygen unsaturation. One of Christie's patients had 90.1 per cent saturation of the arterial blood oxygen and a vital capacity of approximately 1,650 cc. Holman and Shires studied twelve patients with rather marked pulmonary emphysema. The average blood arterial oxygen saturation was 86.6. The average vital capacity was 38.9 per cent normal.

CHAPTER XXVII

THE PREPARATION OF TEST EXTRACTS

Collecting Pollen

Unless one uses large quantities of pollen extract it is more economical to purchase the dried pollen or pollen extracts than to collect and extract it. Three factors enter into this. (a) The time required for field work is considerable; (b) special rooms must be available for collecting the powder and these must not be near rooms frequently occupied by pollen allergies; (c) reliable dry pollen may be purchased at a cost considerably below the cost of collection, considering time expended and space rental.

Bouquet collection.—The flowering heads with some of the stems of anemophilous plants including ragweed, the grasses and the catkin-bearing trees are picked in the late afternoon and carried to the pollen laboratory. This must be a room protected against dust, free from draft, with abundant morning sunlight. In it are flat-topped tables or benches with troughs or other suitable water containers along one side, so built that the bouquets may be placed in them at an angle such that the flowering parts of the plants overhang the unoccupied part of the table. Ordinary mason jars tilted against wooden supports at an angle of 30 or 45 degrees serve nicely. The bouquets are arranged in these containers to be reasonably well spread out and to overhang. Beneath them, large sheets of glazed paper are spread on the tables. Glassine, cellophane, or large glass plates may be used.

The pollen is discharged during the night (grasses) or in the early morning under the stimulus of sunlight. Gentle shaking in the morning increases the yield. A second smaller yield may be obtained on the second day and in the case of some plants, especially the catkin-bearers, the discharge may continue for three or four days. While this applies primarily to anemophilous plants, some entomophilous plants with abundant pollen will shed, as every housewife who has bouquets of coreopsis will attest.

Coca points out that with timothy, orchard grass, rye grass and the catkin-bearing trees water is not necessary. The grass heads and catkins, only, are plucked in the late afternoon and after having been shaken to remove dust, are placed directly on glazed paper. Chief yield with this method is on the following morning although a little more pollen may be shed after 24 hours. After the pollen has been shed onto the glazed surface by either method it is brushed into a pile with a flat camel's hair brush and transferred to a 200 mesh copper sieve, through which it is passed with agitation by means of the brush into a suitable container. Such sieves are available with top cover and collecting base. Otherwise a large porcelain evaporating dish serves well for collecting. The sieve should not be shaken unless it has a tightly fitting cover, otherwise much of the pollen powder may be blown away.

The pollen is next examined microscopically for identification and evidence of contamination (other pollen or dirt), after which the collection is placed in open vials or jars in a glass desiccator over calcium chloride for drying.

Moist pollen usually suffers from mold contamination. After several weeks of desiccation the containers are tightly stoppered and preferably sealed with paraffine, after which they may be stored on any convenient shelf.

Bagging.—In the early morning the collector carries glazed paper bags to the field where he gently bends the flowers of ragweed or the tree catkins into the bag and dislodges the pollen by agitation. Morning rain, dew or strong winds interfere.

The Coca and Milford method.—These investigators recommend the following method for ragweed. Flower heads are collected in the late afternoon and placed in trays with wire netting bottoms which are then placed over the radiator. Suitable baffles are arranged so that hot air from the radiator passes up through the wire screen and rapidly dries the pollen heads. These are then placed in water-free ether which causes the bracts containing the ripened pollen to open, thus releasing pollen into the ether. The pollen is collected by sedimentation and decanting. Following this a mixture of carbon tetrahydrochloride 3 parts, water-free ether 1 part is added. Pollen rises to the top. Contaminating particles sink to the bottom. The floating pollen is decanted. Water-free ether is then added until the grains settle to the bottom. Carbon tetrahydrochloride is removed by several washings in water-free ether. The ether is finally driven off by placing the pollen in a pyrex glass beaker on a hot sand bath. Pollen is stirred until the ether odor disappears. Its temperature should not go over 50° C. Those who have not had the experience of evaporating ether should acquaint themselves with the technic to avoid explosion. The pollen is then dried over calcium chloride as above.

Preparation of Extracts

General principles.—The simplest way in which to test for sensitization to a suspected substance is to test with that substance in its unaltered state. It makes no difference whether it is food, pollen, animal hair or other substance. Earliest skin tests with pollens were made years ago with the granules themselves. The earliest skin tests with foods were done by simply making a scratch on the skin and putting a little of the food, moistened in the form of paste, on the scratch. When investigators realized that the element in the food or other substance responsible for the positive reaction was protein, attempts were made to prepare more potent test materials by isolating and purifying the proteins. This is still the method in general use although since it has been shown that one may be allergic to constituents other than protein, we have often reverted to testing with the natural substance. Patch tests exemplify this.

Many methods have been proposed for making extracts. Often one method is as good as another. In the case of pollens, for example, one can extract the dry powder satisfactorily with physiologic sodium chloride or with an alkaline extracting fluid, such as N/10 NaOH or a weak bicarbonate solution. Ordinary water will do fairly well and body secretions such as the serum exuding after a skin scratch or the tears that follow application of dry pollen to the conjunctiva dissolve enough of the active principle to give positive reactions.

There is a difference in the keeping qualities of various extracts. Molds and bacteria tend to grow in them and for this reason it is better to add some sort of preservative. The four preservatives in general use are alcohol, glucose, phenol and glycerin. Each has its advantages and disadvantages which will be discussed later. The keeping qualities are materially improved with preservatives, some being more effective than others.

As I have stated, the simplest method is to test with the native substance under suspicion. It was next found that the addition of a slight amount of alkali hastened solution of the protein and this is the reason for the use of tenth normal or hundredth normal sodium hydroxide when dry powders are used in scratch testing. Tenth normal concentration is used because it is alkaline enough to dissolve the protein but not so alkaline that it will irritate the skin. Normal sodium hydroxide (10 times as strong) will burn the skin.

The same principle is applied in intracutaneous work. Slight alkalinity seems to favor a good reaction but the solution must not be so alkaline as to be irritating to the tissues. This is the basis of Coca's fluid, a normal physiologic salt solution made slightly alkaline with sodium bicarbonate, to which phenol is added as a preservative. An extract in physiologic sodium chloride would work practically as well intracutaneously, but will tend to deteriorate more rapidly. The carbonate seems to keep the allergen in solution. After an extract in Coca's solution has stood for some time a precipitate often forms which contains some of the active principle. This may be redissolved by blowing carbon dioxide through the solution, restoring the carbonate content.

With strongly acid or strongly alkaline foods, such as meats and fruits, a buffer solution may be used to preserve neutrality. This is available in the form of Evans' fluid or buffered saline.

It has been found that Coca's medium (alkaline extracting fluid) is preferable for pollens, dust and orris root, while buffered saline is used for foods and animal epithelium and danders. Similar extracting fluids in which 15 per cent alcohol is used as a preservative, instead of phenol, are said to deteriorate more rapidly. They are very definitely more painful on intracutaneous testing.

Clock first used glycerin as an extracting medium and as a preservative substitute for phenol and alcohol. A commonly used glycerin extracting fluid is that described by Stier and Hollister, containing 4 per cent sodium chloride, 46 per cent glycerin and 50 per cent distilled water. Hypertonic saline improves extraction by a process akin to that of salting out. Theoretically the increased osmotic pressure of this solution draws the tissue juices out of the substance being extracted. Glycerin extracting fluid is in my experience the most satisfactory for general use. Its chief advantage is its excellent keeping qualities. Alles and Piness report that extracts made by their method which includes glycerin extraction are still potent after 7 years. Extracts with Coca's and Evans' fluids tend to deteriorate rather rapidly, in a matter of a few months. The disadvantage of glycerin is that it is too irritating for intracutaneous use. Endermal irritation gives "false positive" readings. However, glycerin extracts may be made up in concentrated solution which is then diluted at least ten times with physiologic saline, Coca's or Evans' solution for intracutaneous use. Glycerin extracts may be used for hypodermic medication. They are rather painful but usually not distressingly so. Alkaline extracting fluid and buffered saline are not painful. One is therefore faced with the problem, whether to use a solution the potency of which deteriorates rather rapidly but which is not painful when given subcutaneously, or one whose keeping qualities are good but which causes some pain. Unger has suggested dextrose as a preservative. He reports that the keeping qualities are good and that its use causes no pain. This solution has not yet come into wide use. Sullivan and Vaughan (1939) find its keeping qualities superior to Coca's fluid but not as good as those of glycerosaline. Phenol possesses one disadvantage as a preservative in that it causes darkening and precipitation of some extracts, particularly extracts of wheat and rye.

All of these solutions appear therefore to find a place. When tests are being made by the scratch method, glycerin or glycerosaline extracts are generally preferred. When the concentrated extract is being used intracutaneously such as with house dust, which is often feebly allergenic and must therefore be kept as concentrated as possible, Coca's or Evans' fluid is the solution of choice.

For those who prefer to use the commercial dry powders for scratch testing two procedures are available. The dry powder may be applied to the scratch and moistened with tenth normal sodium hydroxide or the dry powder may be suspended in glycerosaline and kept this way as a stock solution or suspension. The testing is made by applying the solution or suspension to the scratch. The latter method has the advantage of saving time. It has the disadvantage that glycerin being slightly irritating to the scarified skin, the negative reaction is not quite as clear cut as with alkali. However with both methods there is equally good differentiation between positive and negative provided one realizes that the negative is not quite as clearly nonreactive with glycerosaline, see Figs. 33 and 34.

A simple method when one does not wish to keep a large quantity of extract on hand consists in pouring the contents of the usual commercial 50 mg. vial of dry powdered extract into 2.5 cc. of a glycerin extracting fluid. This is labeled 2 per cent or 1/50 and is used for scratch testing. Not all of the material goes into solution. It may be filtered, in which case most of the solution is lost on the filter paper, or it may be used as a combined suspension and solution. For endermal testing, a small amount of this solution is diluted 20 times in Coca's fluid and sterilized by passage through a Seitz filter. This is labeled 1:1,000. Assuming the sensitivity of endermal testing to be 100 times greater than that of scratch, and in view of the fact that this endermal extract is 20 times more dilute than the scratch material from which it was derived, the relative reactivity of the two will be as 5 is to 1 in favor of endermal.

Summarizing, the appropriate uses of the various common extracting fluids are as follows:

1. For intracutaneous foods and epidermals a solution in Evans' fluid; or a glycerinated extracting fluid which must however be diluted 10 or 20 times in a nonirritating fluid before use.
2. For intracutaneous testing with pollens, orris root and dust, Coca's fluid; or a glycerinated extract which must be similarly diluted.
3. For scratch tests; glycerinated extracts or dry powders with tenth normal alkali or saline.

The Commoner Extracting Fluids

Buffered saline (Evans). Two concentrated stock solutions are kept, from which the extracting fluid is made by mixing 1 part of solution 1, 1 part of solution 2 and 8 parts of distilled water.

Stock Solution No. 1

NaCl -----	50.00 gm.
KH ₂ PO ₄ -----	3.63 gm.
Na ₂ HPO ₄ ·12H ₂ O -----	14.31 gm.
Distilled water up to 1000 cc.	

Stock Solution No. 2

Carbolic acid, 4 per cent

Alkaline extracting fluid (Coca).—The stock solution is used direct without further dilution, but just prior to use, carbon dioxide gas should be bubbled through it until a drop of phenolphthalein added to a sample no longer turns red.

NaCl -----	5.00 gm.
NaHCO ₃ -----	2.75 gm.
Phenol -----	4.00 cc.
Distilled water to make 1000 cc.	

Gelfand, et al. (1938) find that foaming and sedimentation on Seitz filtration is due to withdrawal of carbon dioxide from Coca's fluid consequent on the reduced gaseous pressure of suction filtration. They found that if positive pressure is used instead, there is no carbon dioxide lost and no consequent foaming or precipitation. This is important since some of the active principle is lost in the precipitated material. It may be recovered by blowing carbon dioxide gas through the solution. The larger Seitz filters are equipped with connections for positive pressure. Gelfand found a pressure of from 10 to 20 pounds satisfactory. Positive pressure produces no loss of CO₂.

Preserving fluid (Coca).—Where the material to be extracted is originally chiefly fluid (fruit and vegetable juices) further dilution is to be avoided. These may be "extracted" and preserved in Coca's fluid which is made five times as strong as the regular fluid. It is then mixed with the fruit or vegetable juice in the proportion of 1 part of preserving fluid to 4 parts of juice. This results in 5 times dilution, the end product being of the same concentration as the regular alkaline extracting fluid.

NaCl -----	25.0 gm.
NaHCO ₃ -----	12.5 gm.
Phenol -----	20.0 cc.
Distilled water to make 1000 cc.	

Glycerosaline (Stier).—The advantages, disadvantages and mode of action of this solution have been discussed above under General Principles.

Glycerin -----	460 cc.
NaCl -----	40 gm.
Distilled water to make 1000 cc.	

Other glycerin extracts. Clock's original fluid (1922) contained $\frac{2}{3}$ glycerin and $\frac{1}{3}$ saturated solution of sodium chloride. Bernton's fluid consists of 2 parts glycerin, 1 part Coca's fluid. Other combinations are $\frac{2}{3}$ glycerin, $\frac{1}{3}$ buffered saline and equal parts of glycerin and physiologic saline.

Dextrose extracting fluid (Unger).—Unger recommended a solution of 5 per cent dextrose in distilled water, with phenol as a preservative. After an extract in this solution stands for a time a sediment of glucoside settles out. Unger and Moore (1936) find that if small amounts of sodium bicarbonate are added the solution remains clear.

Dextrose -----	50 gm.
Sodium bicarbonate -----	27 gm.
Phenol -----	5 cc.
Distilled water to make 1000 cc.	

Piness fluid. The original Piness fluid contained alcohol as a preservative. This is distinctly painful on injection, especially endermally. The more recent preparation described by Alles, Piness and Miller is as follows:

Solution No. 1	KH ₂ PO ₄ -----	40.85 grams per liter
Solution No. 2	K ₂ HPO ₄ -----	52.275 grams per liter
Solution No. 3	C.P. Glycerol	

The standard solution contains 1 volume of solution No. 1, 4 volumes of solution No. 2 and 5 volumes of the glycerol. Although well buffered the solution has a slightly alkaline reaction, pH 7.4, and is isotonic and isohydronic with serum and tissue fluids.

Use by allergists. Alexander found in his survey of the treatment of hay fever by specialists in the United States and Canada that for 28 who used an alkaline extracting fluid of the Coca type, 36 used extracting fluids containing glycerin and 4 used dextrose fluids. Of the 36 using glycerin, 20 combined the glycerin with Coca's fluid in varying proportions. Among 73 different allergists 17 different extracting fluids were used and even within the groups there were undoubtedly different details in the extracting methods. With many the variations are slight and often insignificant. For this reason no effort is made to present a comprehensive discussion of all of the methods that have been recommended. Instead the method that has been found adequate for clinical use in our own laboratory is presented. There is no claim to special originality except in certain of the details, since we, like many others, have availed ourselves of the contributions of other investigators.

METHOD OF PREPARING EXTRACTS

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Our method of food extraction at the Vaughan-Graham Clinic is based primarily on that described by Dr. Milton Cohen of Cleveland to The Association for the Study of Allergy in Kansas City, 1936. Modifications have followed helpful suggestions by Dr. Oscar Swineford, Jr., of Charlottesville, Virginia. Further modifications including especially adjustment of hydrogen ion concentration are our own.

Materials for extraction are obtained in the raw state, or as nearly approximating the raw state as possible. The procedures for extraction strive toward simplification with the view that too vigorous attempts to remove fat, dyes and irritants result in loss of some of the allergenic substances. The stock extracts are made as concentrated as feasible, in order to obviate as much as possible false negative skin reactions and also to conserve storage space.

The method of oil extraction is based primarily upon the work of Coca. However, *Rhus toxicodendron* is extracted according to the methods advocated by Caulfeild and Shelmire and Black.

I. Epidermals

A. Feathers.—Feathers must be obtained directly from the fowl. Precaution must be taken that no blood or water comes in contact with the feathers, and that no quills are used, since there is often blood on the shaft of the quills. The feathers may or may not be ground in the food chopper before weighing. One part by weight of feathers is stirred into 5 parts by volume of the extracting fluid (see Discussion).

The extraction is continued for 48 hours. This should take place either in the ice box or in a cool place with the container covered. At the end of this time the material is placed in an ordinary hand towel and all possible fluid expressed by squeezing. The next step is determination of hydrogen ion concentration. (See Discussion.) The extract is then passed through a Seitz filter and placed in sterile bottles. If desired, culture in dextrose broth for determination of sterility may be carried out. We have not yet obtained growths on extracts following 48 hours' incubation.

The material is now ready for scratch or cutaneous use. For intracutaneous testing it is diluted 10 times with Coca's fluid. Further dilution for hyposensitization is carried out in Coca's fluid.

B. Dog hair, cat hair, rabbit hair, hog hair, cattle hair, horse hair, mule hair, goat hair, camel hair, sheep wool, and horse dander. The animal is clipped or shaved in such a way

ner as to obtain as much hair and dander as possible. It is important that the skin not be made to bleed and that the animal not be scalded.

Just prior to extraction the material is washed with carbon tetrachloride and permitted to dry. It is then weighed and 1 part stirred with 5 parts of extracting fluid. The extraction is permitted to continue for 48 hours with occasional stirring. At the end of this stage fat may be removed by shaking with 3 parts of water-free ether in a separatory funnel. After standing for two hours the fat-free portion is drawn off. All additional steps are carried out as described for feathers.

II. Inhalants

A. Dust.—Ordinary house dust from the bedroom or from other portions of the house is obtained with the vacuum cleaner or broom. It is weighed, washed with carbon tetrachloride and permitted to dry before extraction. One part of the house dust is mixed and stirred with 5 parts of Coca's fluid and extraction is permitted to continue for 24 hours, being carried out in a covered container in the icebox or overlaid with a towel in a cool place. Following this all possible fluid is expressed through a hand towel by squeezing into a Petri dish. The material may be used for scratch as it is or it may be evaporated down to not less than $1/5$ of its volume. If evaporation is carried further than $1/5$ the dust extract should be dialyzed. Sterilization is carried out by use of the Seitz filter. If the scratch or cutaneous test is negative, the same concentration is used for intracutaneous testing. For hyposensitization, various dilutions may be prepared with Coca's fluid.

Bed dust and upholstery dust are treated with carbon tetrachloride just as the house dust. The washed and dried material is then made up into a thick mush with glycerosaline. Following extraction for 24 hours, 1 cc. is diluted with 9 cc. of Coca's fluid. Following sterilization through the Seitz filter, this is used as a concentrated extract, both for scratch and intracutaneous testing.

Boatner, Efron and Dorfman (1940) have described a method of purifying and concentrating the antigenic material in dust which gives an extract of quite uniform, high potency which is quite free of irritative reactions. It is available on the market.*

B. Kapok, cottonseed and flaxseed.—The allergenic substance or substances contained in kapok and cotton may be obtained either from the seed or from fiber. Probably the more concentrated extract is obtained from the seed. However, we use fresh kapok fiber as the seed contains sufficient oil to cause inconvenience in extracting. For cotton and flax the seed is used. Fiber and seed are not extracted in the same manner.

The seed is weighed, mixed and stirred with 5 parts by volume of extracting fluid after grinding in the food chopper or maceration with mortar and pestle. Extraction is continued, with the container covered, for 48 hours. This may be done either in the icebox or in a cool place. All possible fluid is then expressed through a hand towel by pressure. Both fiber and seed contain considerable fat. This is removed by shaking in a separatory funnel with 3 volumes of water-free ether, as described above. However, the mixture must be allowed to stand in the icebox overnight. If the extract is still cloudy, it may be readily cleared up by shaking with more water-free ether. Sterilization is facilitated by Seitz filtration following adjustment of the hydrogen ion concentration. (See Discussion.) The cottonseed extract is ready for scratch or dermal testing, and should be diluted 10 times with Coca's fluid for intracutaneous. However, the flaxseed extract, due to its higher potency, must be diluted 20 times for scratch. Intracutaneous material is made by diluting the scratch solution 10 times, employing Coca's fluid.

C. Kapok and cotton fiber.—The fiber is extracted just as seed except that use of a separatory funnel for fat removal is not necessary. The extracted material is diluted 10 times for scratch and 20 times for intracutaneous testing with Coca's fluid.

D. Orris root.—This material is prepared from powdered Florentine orris root. One weight is mixed and stirred with 5 parts by volume of extracting fluid and the extraction is allowed to continue for 48 hours, in the usual way. The other steps in preparation are identical with those described under feathers.

E. Pyrethrum.—One weight of dried pyrethrum powder is stirred into 5 parts by volume of extracting fluid. The extraction is allowed to continue for 48 hours in the usual way. Additional steps are identical with those described for feathers. Dried flower of the pyrethrum plant may be used. It should be powdered and is extracted just as the dry powder.

*Endo Products, Inc., Richmond Hill, N. Y.

F. Tobacco.—Untreated leaves are used. After grinding, 1 weight of the leaf is mixed and stirred with 5 parts by volume of glycerosaline. The extraction is allowed to continue for 48 hours. Other steps are identical with those used in the preparation of feathers.

G. Tobacco smoke.—Tobacco smoke is extracted over glycerosaline. Suction of the lighted cigarette or cigar is carried out by a hydraulic apparatus designed by the American Tobacco Company and used by us through their courtesy.

H. Silk.—Silk extract is prepared from the silkworm pupa. One part by weight of powdered pupal material or crude cocoon fiber, if the former is not available, is stirred with 5 parts by volume of glycerosaline. Additional steps are identical with those described in making feather extract. This concentration is satisfactory for scratch tests. The scratch solution is diluted 20 times for intracutaneous.

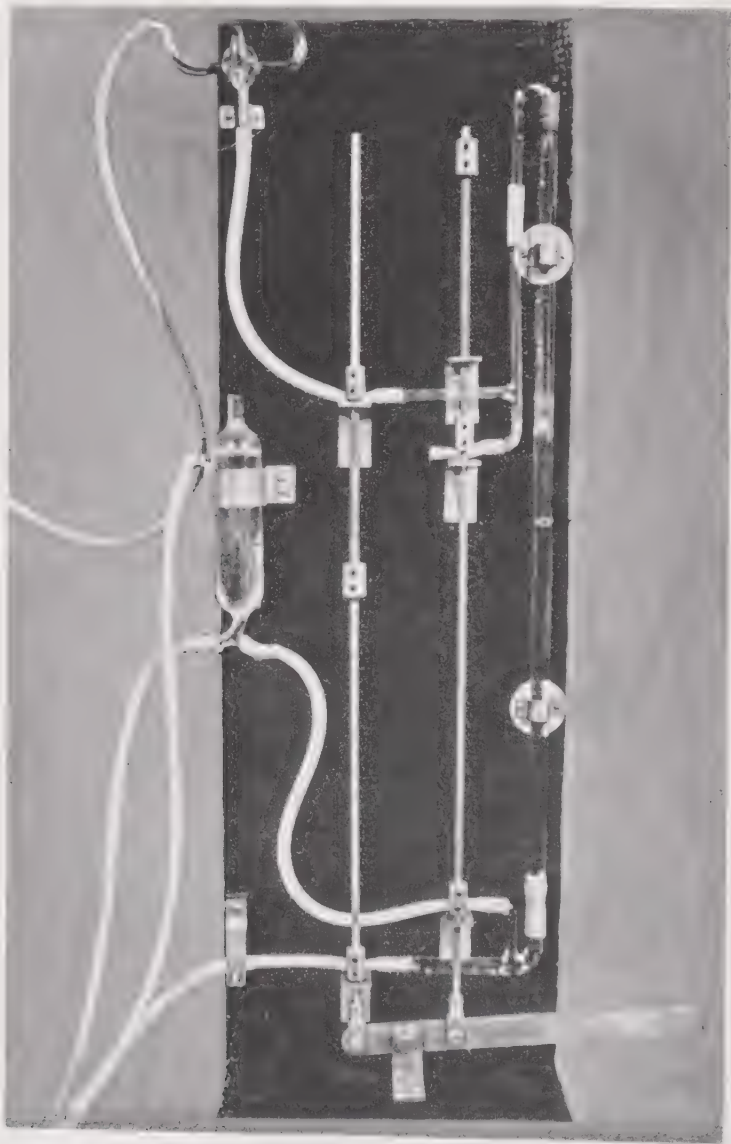


Fig. 53.—Smoking machine. An apparatus developed by the American Tobacco Company for extracting cigarette smoke as produced under normal conditions. The cigarette is attached to a tube at the left. The lever at base is depressed by hand at regular intervals corresponding to intervals of smoking. Each time, an amount of smoke is drawn over the extracting fluid equal to the volume of the average normal inhalation. In this way the same end products are volatilized as in ordinary smoking.

FOODS

I. Cereal Grains

A. Wheat, rye, barley, rice, oats, corn, buckwheat. All of the grains are obtained for extraction in the natural state. In preparing rice, it is better to use the unpolished

grain. Following grinding in the mortar or an ordinary coffee mill, 1 weight is mixed and stirred with 2 parts by volume of extracting fluid. The extraction is carried on for 48 hours, either in the icebox or in a cool dry place, and supernatant liquid is expressed through a towel by squeezing. Determination and adjustment of hydrogen ion concentration is followed by sterilization with the Seitz filter. The concentrated material is used for scratch testing. This is diluted 20 times with Coca's fluid for intracutaneous use.

II. Meats

A. Beef, chicken, veal, pork and lamb.—In the preparation of meat extract it is very important that the specimen for extraction contain as little blood as possible. Mixture of connective tissue with glycerosaline brings about jellying. Therefore, all possible connective tissue should be removed beforehand from the material to be extracted. Fresh meat is obtained and immediately passed through the meat chopper. One weight of meat is mixed and stirred with 2 parts by volume of glycerosaline and extraction is allowed to continue for 48 hours in the icebox. Following this the fluid portion is expressed through a towel by pressure.

In view of the fact that meat extracts contain a large amount of fat, fat removal is carried out in the separatory funnel by shaking the extract with 4 volumes of water-free ether. The mixture must be allowed to stand for at least 1 hour in order to facilitate complete solution of fat. Immediately following removal of fat, the fat-free portion is diluted 1 to 2 times with Coca's fluid to prevent jellying. Determination and adjustment of hydrogen ion concentration and sterilization by Seitzing are carried out as with other food extracts. The undiluted extract is suitable for scratch testing, and is diluted 10 times with Coca's fluid for intracutaneous use.

III. Juicy Fruits

A. Lemon, lime, orange, grapefruit, tomato.—The juice is expressed by means of a press. Two volumes of the juice is mixed with 1 volume of glycerin. After covering the surface with toluol, extraction is carried out for 48 hours, preferably in the icebox. The toluol is then removed by means of the separatory funnel, followed by adjustment of the hydrogen ion concentration and sterilization by Seitzing. This concentration is used for scratch and is diluted 10 times with Coca's fluid for intracutaneous use.

IV. Other Fruits

A. Apple, pear, peach, apricot, prune, pineapple, and banana.—These materials must be obtained and extracted when in season and fresh. The whole fruit is crushed and macerated, with thorough mixing of liquid and solid portions. One part by weight is mixed and stirred with 1 volume of glycerosaline. Other steps in extracting are identical with those described under juicy fruits. Tuft and Blumstein (1944) have shown that the rate of deterioration in these fruits is quite rapid and tests should be done with a 1:5 dilution of the alkalinized fresh juice or its lyophilized extract.

B. Berries, grapes, and cherries.—The material must be obtained and extracted when fresh. After thorough crushing and mixing of solid with fluid portions, 3 parts by weight are mixed and stirred with 1 part by volume of glycerosaline. The mixture is then covered with toluol and extraction is allowed to continue for 48 hours, preferably in the icebox. The material is then squeezed through a towel, toluol removed from that portion thus collected and pH is adjusted. After Seitzing it is diluted 10 times with Coca's fluid for intracutaneous use.

V. Condiments

A. Red pepper, green pepper, mustard, ginger. The pepper pods are obtained and ground whole. Powdered mustard and ginger are used. One part by weight of material is extracted in 1 part by volume of glycerosaline. Other steps are identical with those used for other foods. Since this material is very irritating, it must be diluted 10 times with Coca's fluid for scratch use. The scratch material is diluted 10 more times with Coca's fluid for intracutaneous testing.

B. Black pepper.—Ordinary black pepper is used. It is ground with mortar and pestle and 1 weight extracted in 2 parts by volume of glycerosaline. Other steps are identical with those for red pepper.

VI. Leafy Vegetables

A. Spinach, cabbage, cauliflower, asparagus, turnip greens, mustard greens, lettuce, and okra.—The fresh material is ground in a food chopper, mixing solid and fluid portions. One weight is extracted with 1 part by volume of glycerosaline and additional steps are the same as for other foods. No toluol is used.

VII. Other Foods

A. Walnut, pecan, almond, peanuts, etc.—Untreated nuts are used. The shells are removed and the kernels ground. One weight is stirred into and mixed with 2 parts by volume of glycerosaline, and extraction is continued for 48 hours. Due to the high fat content, defatting is carried out as described for meats. The undiluted material is used for scratch and diluted 10 times with Coca's fluid for intracutaneous testing.

B. Sweet potato, Irish potato, onions, carrots, turnips, etc.—The fresh vegetable is peeled and ground in the food chopper. One weight is mixed with 1 part by volume of extracting fluid and left for 48 hours, followed by adjusting of pH and Seitzing. The undiluted material is suitable for scratch and is diluted 10 times with Coca's fluid for intracutaneous use.

C. Peas and Beans.—The material is prepared from untreated seed, and it is advisable to purchase them from seed merchants. They are ground into a fine meal and 1 weight is extracted for 48 hours in 3 parts by volume of glycerosaline. It is then expressed through a towel and defatted. Additional steps are identical with those described for other foods. The undiluted material is used for scratch, and is diluted 10 times with Coca's fluid for intracutaneous use.

VIII. Milk

Eight hundred cc. of fresh skimmed milk is required for extraction. The first step in preparation is removal of casein. This is done by dropping into the skimmed milk $2\frac{1}{2}$ cc. of 1 per cent rennin or an ordinary commercial junket tablet. At once the milk with rennin is placed in an incubator at 37° C. for 30 minutes, care being taken not to stir it. At this time the whey and clabber will have separated. The clabber, which contains the casein, is removed by filtering through a towel in the usual way, and then refiltering through ordinary filter paper. The resulting filtrate contains the lactalbumin.

Precipitation of lactalbumin from the whey is done by the adding of 3 volumes of acetone to the filtrate and placing in the icebox for 24 hours. Following this as much of the supernatant fluid is poured off as possible and discarded. The remaining filtrate is further separated by several minutes of centrifugation. Precipitate is then placed in a mortar and washed with several changes of acetone, and then powdered, to be placed in the incubator and left to become as dry as possible. One weight of the dried powder is stirred with 50 parts by volume of glycerosaline and the extraction is allowed to continue for 48 hours. The other steps in preparation are the same as those described for other extracts. This concentration is suitable for scratch testing and is diluted 20 times with Coca's fluid for intracutaneous use.

IX. Eggs

The egg white and egg yolk are separated. The yolk is mixed and stirred with 10 parts by volume of the glycerosaline and extraction is allowed to continue for 48 hours, preferably in the icebox. Following this, fat is removed in the usual manner and sterilization is done by Seitzing. The resulting concentration may be used for scratch, and is diluted 20 times with Coca's fluid for endermal testing.

Any part of egg is extremely difficult to pass through the Seitz filter; however, the filter should not be heated in order to hasten filtration. Patience is required and eventually the extract will come through.

Egg white is diluted 10 times by volume with glycerosaline and allowed to extract in the icebox for 48 hours. The material is then Seitzed and the resulting concentration used for scratch tests. To further obviate reactions from intracutaneous testing, the scratch material of egg white is diluted 100 times with Coca's fluid and allowed to stand in the icebox for 48 hours. This material is then passed through the Seitz filter and is used for endermal testing. In cases of suspected egg sensitivity, it is still further diluted 20 times with Coca's fluid before testing intracutaneously.

X. Cocoa and Coffee

The bean of either cocoa or coffee is used. After grinding in the ordinary coffee mill, 1 weight of material is stirred and mixed with 5 volumes of glycerosaline. The other steps in preparation are identical with those described for peas and beans. The undiluted material is used for scratch testing and is diluted 10 times with Coca's fluid for intracutaneous use.

XI. Oil Extracts

For extraction of all oils, except poison ivy, the method of Coca is used.

Sufficient U.S.P. acetone is added to the material in a jar to be able to saturate as well as bathe and cover. A top is placed on the jar and following thorough stirring it is allowed to remain for 48 hours. It is best to stir the extracting material 6 or 8 times during the 48 hours. Following this, all available liquid is poured into a Petri dish or evaporating dish. Deacetoneization is facilitated by either evaporation in the icebox or by direct blow from an electric fan. This depends upon whether extraction takes place in winter or summer. After all acetone has evaporated, there will remain a very viscid deposit. This is the oil extract. Next, by quite gentle heating with the microburner, just sufficient almond oil, which has been sterilized in the autoclave, is poured into and mixed with the oil extract and stirred to the point of complete solution. Care must be taken to avoid using the oil in excess. This material is diluted 10 times with sterile almond oil for patch testing.

Poison ivy (*Rhus toxicodendron*).—Enough of the ivy leaf is collected to fill a pint jar. It is essential that care be taken not to permit the plant to come in contact with the skin. This is obviated by using household rubber gloves and inexpensive scissors all of which can be thrown away after gathering the ivy. Similar precautions should be taken during extraction.

Sufficient water-free ether is poured into the jar to saturate the leaves. This is allowed to remain for 48 hours, following which all available liquid is poured into a dish for evaporation. During the period of extraction the material may be mashed several times with an applicator or a stick.

Further steps are identical with those for other oil extracts except that corn oil which has been sterilized in the autoclave, as suggested by Caulfeild, is used. Stock solution is made up in dilution of 1/5. Patch material is diluted 1/25.

Discussion

Glycerosaline (Stier-Hollister) is used in the extraction of all materials with the single exception of house dust. Coca's fluid is employed in the extraction of house dust, since concentration by evaporation may be necessary. Mattress dust, bed dust, upholstery dust, bookcase dust, card file dust, etc., are collected in too small quantities for evaporation of the extract. Therefore, glycerosaline is found more suitable for their extraction.

Due to its superior preservative qualities, glycerosaline is used as a diluent for all pollens. All other extracts are diluted with Coca's fluid. However, glycerosaline is frequently found to be quite painful when administered subcutaneously and in such cases the pollen is diluted with Coca's fluid. Glycerosaline is preferable for dilution of pollen extract in order to assure minimum deterioration. This is not so important a factor with the inhalants and ingestants; therefore, Coca's fluid is used, thus obviating much of the discomfort of injection.

For the bacteria, fungi and yeasts, carbolyzed saline is used.

It is important to maintain the hydrogen ion concentration as nearly neutral as possible. This is adjusted as nearly to 7 as possible by addition of sodium hydroxide or hydrochloric acid, as indicated, to the stock extracts. They should be checked at least every two months. All hydrogen ion concentration determinations and adjustments are carried out under sterile precautions. Nitrazine paper (Squibb) may be used.

Standardization of Extracts

Total nitrogen determination. The importance of nitrogen determination in the standardization of allergen extract is becoming increasingly recognized. While, as shown by Alexander, the most generally used method of making

up pollen extracts is by the weight-volume or percentage method, the fact remains that the actual concentration of active allergen remains unknown. While the margin of error for successful therapy is sufficiently wide so that this is usually not a factor of importance in clinical work, the fact remains that the more scientifically accurate method of standardization of allergen extract is based on protein and nitrogen content. Such standardization is usually a prerequisite to acceptable quantitative investigative work.

For this reason the development of reliable micromethods for the determination of total nitrogen and nonprotein nitrogen is of distinct aid in allergic work. Cohen and Goodale (1933) have described a method for the determination of total nitrogen in various allergen extracts, based upon the technic of Hubbard and Sly for the determination of serum protein. They describe their method as follows:

Apparatus.—Digestion tube, 200 mm. by 24 mm., resistance glass; graduated at 35 and 50 ml.; watch glass 25 mm. diameter; micro-Bunsen burner equipped with a chimney to protect the flame; four 1 ml. pipettes (Ostwald).

Solutions.—1. DIGESTION MIXTURE.—Either one of the following may be used:

Sulfuric-copper sulfate mixture.—To 10 cc. of 5 per cent copper sulfate solution add 100 cc. of concentrated sulfuric acid. Carefully pour this mixture into 100 cc. of distilled water, stirring constantly.

Phosphoric-sulfuric mixture.—To 50 cc. of a 5 per cent copper sulfate solution add 300 cc. of 85 per cent phosphoric acid and mix. Add 100 cc. of concentrated sulfuric acid free from the least trace of ammonia, and mix. Keep well protected to prevent absorption of ammonia from the air. Dilute 1:1 with distilled water for use.

Either one of these mixtures may be used. The sulfuric-copper sulfate solution gives less precipitate and is probably a little better for general use. The phosphoric-sulfuric mixture is a more rapid digestion solution.

2. NESSLER'S SOLUTION.—Introduce into a 500 cc. Florence flask 150 gm. potassium iodide and 110 gm. of iodine, add 100 c.c. of water and an excess of metallic mercury (140-150 gm.). Shake the flask continuously and vigorously for seven to fifteen minutes or until the dissolved iodine has nearly all disappeared. The solution becomes quite hot. When the red iodine solution has become visibly pale, though still red, cool in running water and continue the shaking until the reddish color of the iodine has been replaced by the greenish color of the double iodide. The whole operation does not usually take more than fifteen minutes. Decant the solution, washing the mercury and flask with liberal quantities of distilled water. Dilute solution and washings to 2 liters. If the cooling was begun in time, the resulting reagent is clear enough for immediate dilution with 10 per cent alkali and water, and the finished solution can be used at once for nesslerization. From this stock solution of potassium mercuric iodide prepare final Nessler's solution (containing about 55 gm. per 100 cc.) which has been allowed to stand until the carbonate has settled, the clear solution being decanted and used. This solution may be purchased commercially if desired.

3. TEN PER CENT SOLUTION OF ROCHELLE SALTS.

4. STANDARD NITROGEN SOLUTION.*—Dissolve and dilute 0.1414 gm. of the purest ammonium sulfate to 100 cc. with distilled water (5 cc. equals 1.5 mg. N). Dilute 50 cc. of this stock solution to 150 cc. with distilled water, making a convenient standard for use (1 cc. equals 0.1 mg. N.).

Procedure.—The protein extract is diluted with distilled water so that 1 cc. of the solution will equal approximately 0.1 mg. of nitrogen per cc. (the strength of the standard). Reference to Table XXII shows the dilutions found convenient in some typical instances.

After the extract is properly diluted, mix the following in a digestion tube: 1 cc. of extract, 1 cc. of digestion mixture.

Heat slowly on the micro-Bunsen burner until the water boils off and white fumes appear, and then cover the tube with a watch glass. Continue to heat until the solution

*This standard may be purchased from Hartman-Ledden Co., Philadelphia, Pa., 5 ml. containing 1 mg. nitrogen. Dilute this solution 50 ml. to 100 ml. then 1 ml. will contain 0.1 mg. nitrogen.

first chars and then becomes clear white (a faint green tint may be present). Remove the flame and allow to cool for thirty seconds. Add slowly, drop by drop, about 5 cc. of distilled water and then 1 cc. of the 10 per cent Rochelle salts solution. Add distilled water up to the 35 cc. mark. At this point the tubes may be corked and kept in a refrigerator for twenty-four hours, if desired.

TABLE XXII

SUBSTANCE	AMOUNT USED	AMOUNT OF EXTRACTING FLUID	APPROX. N. PER CC.	APPROX. DILUTION REQUIRED
Orris root	460 gm.	1900 c.c.	0.18 mg. per cc.	1-1 (6)
Horse dander	*	*	3.3 mg. per cc.	1-30
Cat hair	*	*	0.37 mg. per cc.	1-3
Feathers	†	†	1.0 mg. per cc.	1-10
Goat hair	†	†	0.1 mg. per cc.	None
Rabbit hair	*	*	0.05 mg. per cc.	None
Wool	†	†	0.1 mg. per cc.	None
Mustard	1 lb.	1000 cc.	6.4 mg. per cc.	1-64 (6)
Cottonseed	40 gm.	1000 cc.	2.3 mg. per cc.	1-23 (6)
Flaxseed	40 gm.	1000 cc.	0.23 mg. per cc.	1-2
Glue	100 gm.	1000 cc.	6.64 mg. per cc.	1-66
Milk (casein free)	100 cc.	100 cc.	0.5 mg. per cc.	1-5
Wheat	350 gm.	2600 cc.	0.75 mg. per cc.	1-7 (6)
Rice polished	225 gm.	2000 cc.	0.3 mg. per cc.	1-3 (6)
Rye	145 gm.	400 cc.	1.0 mg. per cc.	1-10 (6)
Oats	*	*	1.6 mg. per cc.	1-16
Cornmeal	708 gm.	600 cc.	0.45 mg. per cc.	1-4 (6)
Meats	1 lb.	1000 cc.	3.0 mg. per cc.	1-30
Tea	*	*	1.0 mg. per cc.	1-10
Chocolate	*	*	1.0 mg. per cc.	1-10
Barley	*	*	1.0 mg. per cc.	1-10
Peanut	*	*	5.0 mg. per cc.	1-50
Pollens	3 gm.	100 cc.	0.3 to 0.6 mg. per cc.	1-5

*Because some substances vary to such an extent in the amount of nitrogen which may be extracted from them, it is sometimes advisable just to saturate the substance with the extracting fluid. These extracts were produced in this manner.

†These substances are extracted with difficulty so that after the first extraction is made, and extract removed, more of the substance to be extracted is placed into this same extract, thus increasing the atopen content of the final extract.

Reading.—Standard—1 cc. standard nitrogen solution; 1 cc. digestion mixture; distilled water up to the 35 cc. mark; 15 cc. Nessler's solution. Mix by inverting the tube. To the extract add 15 cc. of Nessler's solution. Read the extract against the standard in a colorimeter preferably by daylight.

Calculation.—
$$\frac{\text{Colorimeter reading of Standard}}{\text{Colorimeter reading of Extract}} \times 0.1 \text{ (amount of nitrogen in standard)} \times \text{dilution} = \text{milligrams nitrogen per cc. of extract.}$$

Protein nitrogen standardization. There is still considerable divergency of opinion regarding the most satisfactory method of standardization of pollen extracts. The Noon weight by volume method has the inherent disadvantage that the allergenic substance in a given weight of pollen varies from year to year. The Clock method of standardization by complement fixation capacity against antipollen serum, possesses the disadvantage that there are several proteins in pollen, only some of which are allergenic. This method measures all the proteins.

Cooke and Stull raised this same criticism against the total nitrogen method of standardization previously recommended by Cooke, and have proposed a protein nitrogen method. Here again all of the proteins, including allergenic and nonallergenic, are included in the unit, but since nonprotein nitrogen, presumably nonallergenic, may represent as much as two-thirds of the total nitrogen, it becomes obvious that the determination of protein nitrogen is theoretically a nearer approach to accuracy.

Cooke and Stull prepare their extract as follows:

A weighed amount of dry pollen is defatted in Soxhlet with petroleum ether or C.P. anhydrous ether. The ether extract may be used for the preparation of the fat soluble antigen of pollen which sometimes causes pollen dermatitis.

From 3 to 12 grams per 100 cc. of dried defatted pollen is extracted in alkaline saline extracting fluid (Coca). Extraction is continued for a few hours, not more than 18, at icebox temperature.

The extract is then filtered through paper, subsequently through Seitz or Berkefeld filters. It is tested for sterility, following which protein nitrogen content is determined.

Protein nitrogen determination. First determine the total nitrogen in 5 to 10 cc. portions of the concentrated pollen extract, by the Kjeldahl method. Next, determine nonprotein nitrogen by the usual method of precipitation with phosphotungstic acid. To 10 cc. of the concentrated extract, add 2.5 cc. of concentrated hydrochloric acid and approximately 1 cc. of 10 per cent phosphotungstic acid in 10 per cent hydrochloric acid solution. This precipitates the protein, leaving the nonprotein nitrogen in solution. The solution should be shaken and allowed to stand for 2 hours after which the precipitate is filtered off and washed free of nonprotein nitrogen. Kjeldahl determination of the filtrate and washing gives the nonprotein content. This, subtracted from the total nitrogen, gives the figure for the protein nitrogen. Cooke and Stull state that with 3 to 4 grams of pollen per 100 cc. sufficient nitrogen will be present in the extract for determination. This method may also be used for glycerin extracts. Extracts should not be filtered subsequent to protein nitrogen determination, since some of the active extract is removed by filtration.

According to Stull, Cooke and Tennant protein nitrogen may be determined direct. For this they use defatted pollen, the oils having been removed with anhydrous ethyl ether. The technic is satisfactory for aqueous extracts, extracts in alkaline extracting fluid, and glycerosaline extracts. They found extraction to be quantitative in concentrations ranging from 1 to 9 per cent. That is, a 9 per cent extract contains 9 times as much protein nitrogen as a 1 per cent extract. This may or may not hold true for stronger concentrations, 9 per cent being the highest studied.

The technic is as follows: Suspend a weighed amount of defatted dry pollen in a known volume of appropriate extracting fluid. Use at least 1 per cent concentration. Allow this to extract with occasional shaking for at least 3 hours at icebox temperature, 7° C. Filter. Slightly acidify the filtrate (pollen extract) with 10 per cent HCl. Place 10 cc. in a dry test tube.

Add an excess (about 1 cc.) of 10 per cent phosphotungstic acid in 10 per cent hydrochloric acid solution.

Allow precipitate to settle. Centrifuge. Decant supernatant fluid containing nonprotein nitrogen. Wash the precipitate three times with 10 per cent HCl containing 0.5 per cent phosphotungstic acid, by repeated centrifuging.

Dissolve precipitate in 1 per cent sodium hydroxide.

Transfer to a digestion flask.

Perform a Kjeldahl nitrogen determination.

This gives directly the protein nitrogen content of the extract.

It is important for clinical use that the determination be made after Seitz filtration if Seitz filtration is to be used. A certain amount of the active principle is adsorbed onto the filter, thereby reducing the activity of the extract. It has been shown that re-filtering through a Seitz four times completely destroys the antigenic activity of a pollen extract.

Anhydrous alcohol-free ether is necessary because it has been shown that alcohol removes part of the active substances. Rapid washing with 85 per cent alcohol, with subsequent extraction with ethyl ether, removes one-third of the nitrogen of extract of untreated pollen.

There is still no unanimity of opinion with regard to the relative merits of the total nitrogen standard and the protein nitrogen standard. Bowman has presented evidence that the latter is not as reliable as claimed. She found no correlation between the activity of the extract and the protein nitrogen content. An extract which contained 65 per cent as much protein nitrogen as another standard extract only showed 10 per cent as much activity by skin test.

Since both total and protein nitrogen standards are used by competent investigators; since neither is above criticism; and since both represent greater accuracy than the weight-volume standard, it would appear that one is as acceptable as the other, for the present, as a quantitative standard for investigative use.

Total nitrogen determination in glycerin extracts.—Glycerin interferes with the determination of total nitrogen by the usual method. Digestion must be continued for a much longer period. The writer is indebted to Major R. L. Holt* for the following method for the determination of total nitrogen in glycerin extract.

Take 1 cc. of extract
Add 1 cc. Acid Digestion Mixture
Add 2 gm. Potassium Persulfate
(Merck's C.P. for N determination)

Heat over microburner until white fumes begin to appear. Cover and heat slowly for 30 minutes. Cool.

Add, carefully, 2 cc. distilled water and 2 gm. of potassium persulfate, heat slowly 30 minutes with tube covered. Repeat this process three times more.

At last add 2 cc. water and some alizarin. Connect to a flask containing 20 cc. of N/50 HCl. Add 40 per cent NaOH through a thistle tube until the alizarin shows slight alkalinization of the tube in which the extract has been digested. Then add 2 cc. more. About 5 cc. are required in all. Heat the mixture slowly and carefully until all NH_4OH has been distilled into the HCl solution. Titrate back the HCl. Figure amount combined and, from that, the N in the extract. This is the total N.

Potency of concentrated extracts.—There has been some difference of opinion as to the potency of high concentrations of pollen extract. In the opinion of many allergists 2 or 3 per cent concentration represents the most desirable high concentration for testing and therapy. Higher concentrations with higher nitrogen content can be made but in the opinion of some, antigenic capacity does not increase proportionately above 3 per cent. Thus a 6 per cent extract will not give a skin reaction twice as large as a 3 per cent extract and a 12 per cent extract will not give one four times as large as that from a 3 per cent extract. G. T. Brown, however, believes that pollen extracts may be made the potency of which increases with the concentration up to a concentration of 12.5 per cent.

Rappaport has recently shown that an extract may be made up to 18 per cent concentration, in which the antigenic activity is comparable to the concentration. He extracted ragweed in distilled water and evaporated this dry, over a period of 24 hours in a special apparatus which provided filtered air at 40°C . After a period of storage, the dry residue was completely redissolved, the entire original nitrogen content being again obtained in the more concentrated subsequent solution. When this purified solution was diluted to nitrogen contents comparable to those used in skin testing and treatment, it was found that the sizes of the positive reactions corresponded and that the two substances could be used interchangeably in treatment without any untoward reaction which would indicate differences in potencies.

*Holt, Major R. L.: Army Medical Center, Washington, D. C.

We may conclude therefore that with special methods pollens may be extracted up to a concentration of 18 per cent and that under these conditions percentage concentration corresponds to the relative potency.

Effect of heat on pollen allergen. The stability of the antigens commonly used in allergic work is rather surprising. Black boiled pollen extract for ten minutes without diminishing its potency. Gay found that short ragweed lost some potency after boiling.

Rappaport found that egg albumin was not altered as regards solubility or antigenicity as indicated by skin reactions, following exposure to dry heat for two hours at 140° C. Incidentally this heat destroyed spores of *B. subtilis* in the egg albumin.

Giant and short ragweed (dry) exposed to 140° C. for two hours lost about one-third of nitrogen content, but when made into solutions of the same nitrogen content as that of unheated pollen extract, showed no diminution of antigenic activity.

PART V

THE DIAGNOSIS AND TREATMENT OF FOOD ALLERGY

To me it appears . . . that nobody would have sought for medicine at all, provided the same kinds of diet had suited with men in sickness as in good health. . . . For cheese does not prove equally injurious to all men, for there are some who can take it to satiety without being hurt by it in the least, but on the contrary it is wonderful the strength it imparts to those with whom it agrees; but there are some who do not bear it well, their constitutions are different, and they differ in this respect, that what in their body is incompatible with cheese is aroused and put in commotion by such a thing; and those in whose bodies such a humor happens to prevail in greater quantity and intensity, are likely to suffer the more from it. But if cheese had been pernicious to the whole nature of man, it would have hurt all.

—HIPPOCRATES.

CHAPTER XXVIII

THE DIAGNOSTIC PROGRAM IN FOOD ALLERGY

The diagnostic measures employed in the study of food allergy have been discussed in previous chapters. We shall discuss here their application in the individual case.

Food idiosyncrasy has probably been recognized since the earliest time at which man could reason and recognize a cause-and-effect relationship between repeated ingestion of a certain food and subsequent illness. It is not surprising that the writer has found no Biblical references to illnesses that could be considered allergic. The Bible, representing the folklore of the people, handed down from priest to priest by word of mouth for hundreds of years before it was reduced to the written word, would scarcely be expected to contain mention of transient allergic episodes in individuals.

It is intriguing although hazardous to consider the possibility of food allergy as the reason for Emperor Shen Nung's direction (3,000 B.C.) that the pregnant woman should not eat fish, shrimp, chicken or horse meat since they are likely to produce ulceration of the skin.

The expression, "One man's food is another's poison," represents the cumulative experience of many generations. The phraseology of Lucretius (96 to 55 B.C.) would indicate that he was a better observer of nature than those who today misquote him. He did not write, "One man's food is another's poison." Instead he wrote, "One man's food *might be* another's poison." This clearly demonstrates his recognition two thousand years ago of the phenomenon which today we term food idiosyncrasy.

The terms idiosyncrasy and allergy have a very similar connotation, the former indicating a reaction peculiar to the individual, the latter an altered or individualized capability for reaction. However, it is only within the last thirty years that a possible connection was recognized between the old food idiosyncrasy and the phenomena of anaphylaxis. Seven years elapsed following Richet's description of his findings before Doerr suggested this relationship. Even so, many continued to insist that the two were basically different.

Evolution of food testing.—Early European studies of the relationship dealt with the response of the individual to ingestion of substances which were known to cause symptoms. This included occasional foods such as seafoods, and cases of extreme sensitization to commoner substances such as egg and milk. Early in the study skin tests were applied with extracts of *known* offenders. Chief interest was in the character of the skin reaction as a new and interesting phenomenon. Schloss, in this country, first used the skin test as a *diagnostic* measure, applying a series of extracts with the aim of discovering the etiologic agent. This was in a measure the reverse of the former procedure. The earlier work having demonstrated that the reaction to allergens consisted in the formation of an urticarial wheal, a phenomenon which did not occur with nonallergenic substances, the test was then applied with suspected foods, watch being kept for the diagnostic wheals.

Scratch vs. endermal. In a sense two schools now developed: those who performed tests by preference in the manner first promulgated by Schloss and by Walker, that is, the scratch test; and those who placed greater confidence in the endermal method as developed especially by Cooke. The early literature of skin testing reflects rather considerable difference of opinion as to the relative merits of the two methods. Today the value of both is recognized and both are used in their proper place by the majority of allergists. Much of the confusion was removed by the work of Fineman who showed that in general the endermal test represents approximately 100 times the reactivity of the scratch test. If the scratch test is made with a 1:50 extract and is compared with the 1:5,000 endermal test (100 times more dilute), the reactions are comparable, and the relative advantages are roughly equal. A very dilute intracutaneous test extract therefore has little or no advantage over a concentrated scratch extract.

Combined use.—If we are to derive maximum information from skin tests with foods, we should avail ourselves of the advantages inherent in both testing methods. This is done by first testing cutaneously, with subsequent intracutaneous testing with the same foods. The scratch method is far safer. So far as the writer has been able to determine only two anaphylactic catastrophes with death have been reported following scratch testing. Many more have followed endermal testing. In order to obviate this source of difficulty in endermal testing, many of the endermal extracts available are made so dilute, as a safety precaution, that they lose any possible advantage. If, however, scratch tests are done first, and those food extracts which have given positive scratch reactions are removed from the endermal test set, repetition will then be made only with those extracts which have been negative, or at most, borderline by scratch. In this way a stronger endermal extract may be used than would be otherwise safe. Assuming the use of a 1:50 or 2 per cent scratch extract, one may use a 1:500 endermal extract provided tests are made only to those foods which have failed to give definite positive scratch reactions. This extract is ten times more dilute, but since the endermal reactivity is 100 times greater, the result is a ten times greater reactivity. In my experience this is entirely safe

provided the precaution is always taken of not testing with substances which have already shown up as definitely positive by scratch. The information having been obtained from the scratch test, there is no need for repeating it intracutaneously. Other substances which are feebly allergenic or to which the patient reacts only in low degree, may have given so-called false negative scratch reactions. The ten times greater reactivity of the endermal test will enable the examiner to recognize some of these, in this manner eliminating a certain proportion of false negative reactions.

Anamnesis.—As a preliminary to skin testing there should be a comprehensive discussion with the patient concerning his allergic experiences. Careful questioning should elicit all episodes in the past experience which might be of allergic origin. Special attention should be given to foods which the patient has suspected. Certain foods are so frequently responsible for sporadic or intermittent allergic episodes that specific questioning concerning them will not infrequently recall the fact to the patient. These foods include such as cabbage, onion, cucumber, strawberries, tomatoes, chocolate, nuts and shellfish. Symptoms caused or suspected as being caused by these and other foods should be recorded.

At the completion of the discussion, the patient should fill out an idiosyncrasy list (page 151). It is surprising how a patient will often recall some particular food, usually one rarely eaten, such as mushrooms, cranberry, Coca-Cola, yeast cakes, oysters, only after his memory has been refreshed by seeing the name of the food in such a list.

Food dislikes.—The patient should indicate on the list not only those foods which he is sure cause trouble but also those which he suspects. These will be compared later with the results of objective testing. He should record those foods which he dislikes. Rowe has emphasized that the dislike of a food is often a protective measure, associated with allergy thereto. My own experience has been rather different. We find that more often the patient is unusually fond of the food which causes symptoms. In a series studied by Vaughan and Pipes, there was a 20 per cent correlation between food dislikes and food allergy. Among 80 per cent of allergies there was no correlation between dislikes and foods causing allergy.

Among allergic individuals 4.8 per cent of foods described as disliked are recognized by the patient as provocative of symptoms (anamnesic group). Among allergic individuals 12.7 per cent of foods mentioned as disliked gave positive or borderline skin reactions.

Approximately 80 per cent of persons, allergic or nonallergic, have one or several food dislikes.

While foods disliked may be responsible for food allergy, this is not the rule, and foods disliked cannot be relied upon as indicative of allergic sensitization. The one outstanding exception is in those cases in which gastrointestinal symptoms follow the ingestion of the allergenic food after such a short interval that the patient has himself recognized a cause-and-effect relationship.

This is well illustrated in the study by Williams (1936) of 150 school children who refused, or showed a disinclination, to take milk at school. Fifty-eight and seven-tenths per cent refused because its ingestion was always followed by allergic manifestations of some sort. Almost without exception symptoms were gastrointestinal. Of the 88, nausea was the complaint among 47; vomiting in 37; severe abdominal pain in 1. The only 2 who did not have gastrointestinal

symptoms had asthma and eczema. Among those who reacted with vomiting, 14 had accompanying migraine. Twenty-four per cent of the total number disliked milk but had no symptoms from it. Williams found a personal or family allergic history in all except 4 in this group, and concluded from this that aversion to milk may be subconsciously protective. However, so many families have a history of allergy that such conclusions are questionable. The remainder of the children gave reasons not connected with possible allergy.

Check list of foods eaten.—For future reference, the patient should check a list of foods, indicating the frequency with which he eats them. For this purpose the modified Ellis form (page 144) serves adequately. Major foods are listed according to the biologic food grouping, for ready comparison with the skin test forms and with the idiosyncrasy list (page 151). Since each has his own food preferences, major foods for one person may differ from those for another. The check list of foods enables one to determine at a glance the general character of the patient's diet. Possible deficiencies in one or another of the food elements are usually easily recognized. In general, when symptoms are more or less continuous, special attention should be given to those foods which are checked as being eaten frequently. When symptoms are intermittent, as in migraine, recurrent urticaria or angioneurotic edema, equal attention will be given to occasional foods. However, since allergy to foods eaten daily may play a part when symptoms are only intermittent, both groups should receive attention. Likewise, when symptoms are rather continuous, we have found that, in addition to sensitization to daily foods, the patient is usually also allergic to occasional ones. This has been brought out in our discussion of minor allergy in which the patient is usually sensitized to occasional foods and apparently not to daily foods. In major allergy, where daily contact substances are most important, the patient is at the same time allergic to occasional substances and in approximately the same frequency as is the minor allergic. As far as occasional foods are concerned both groups react similarly. It becomes obvious that, whether symptoms are continuous or intermittent, one should study both the foods which are eaten regularly and those which are taken only upon occasion.

Recheck on anamnesis. Following discussion with the patient, filling out of the idiosyncrasy questionnaire and the check list of foods, and the performance of the skin tests, first by scratch and later to negative or borderline foods by endermal testing, one should now review the results with the patient. Skin testing is by no means a one hundred per cent reliable measure of active sensitization. So-called false negative and false positive reactions occur in nearly every case, but it is surprising how frequently a patient, after having seen the results of testing, will recall that certain of the positively reacting foods have at times caused symptoms. This will happen in spite of the precautions that have been taken in the questioning and in the filling out of the idiosyncrasy list, to be sure that the patient records all suspects. It has been our custom to record these final anamnestic observations by the patient as marginal notations on the skin test form. No other notations appear on this form. They indicate that the information was obtained only after the patient had seen that these foods reacted positively. Further study may show that the patient's recognition of a positively reacting food was erroneous and that the particular food does not cause trouble. But usually the reverse is true and under any circumstance the information should be recorded for future reference.

Reliability of skin testing.—Unfortunately skin testing with food extracts does not have as high accuracy as does testing with inhalants. False negative

and false positive reactions are far more numerous. Alexander, likewise Rowe, finds about 50 per cent accuracy with food testing. In a series of migraine cases, the writer also found approximately 50 per cent correspondence between positive and negative skin reactions and the presence or absence of allergic response. In another study in which the skin response was compared with the leukopenic index and with known allergy to the foods tested, we observed 64 per cent reliability in the skin test. Even this leaves much to be desired. In an effort to develop collateral objective methods for the diagnosis of food allergy, the writer has applied the available knowledge of the biologic relationships of foods and has developed the leukopenic index and the food diary as helpful measures. These, with Rowe's elimination diets, are accessory methods, the employment of which materially enhances the accuracy of diagnostic work in this phase of allergy.

TABLE XXIII. POSITIVE SKIN REACTIONS IN A SINGLE CASE SHOWING VARIATIONS FROM YEAR TO YEAR

FOODS	1923	1925	1926	1928	1930	1931	1935	FOODS	1923	1925	1926	1928	1930	1931	1935
	16, NOV.	19, NOV.	2, DEC.	24, MAY	26, MAY	2, OCT.	30, DEC.		16, NOV.	19, NOV.	2, DEC.	24, MAY	26, MAY	2, OCT.	30, DEC.
1. Wheat	2			0			2	26. Bean	1			1	3	?	0
2. Wheat gliadin	0	0		0			2	27. Lemon				0	1	0	0
3. Wheat globulin	1			0	0	0	3	28. Grapefruit	0	0		2	?	0	0
4. Wheat glutenin				0	0	0	0	29. Orange	0	0		0	0	3	1
5. Wheat proteose				1	0	0	2	30. Grape	0	?	1		1	0	1
6. Wheat leucosin	?			0	1	0	2	31. Okra					1	0	0
7. Barley				0	0	0	2	32. Cocoa	2		0	0	0	0	0
8. Oat	?			?	0	0	0	33. Tea	?				0	0	2
9. Rice	?			0	1	0	0	34. Celery	0	0		0	1	0	0
10. Corn	0	?		0	?	2	0	35. Carrot	2			0	?	?	0
11. Cocoanut	?	0			0	0	0	36. Tomato	3			2	3	0	0
12. Pineapple	1			0	0	0	0	37. Pepper			2	1	?	0	0
13. Asparagus	2			0	0	2	2	38. Squash	0	?		2	1	?	0
14. Banana	0	0		0	0	0	1	39. Lettuce	?			?	0	0	2
15. Buckwheat	0	0		0	0	0	2	40. Milk	0	0		0		0	1
16. Turnip				0	0	0	1	41. Lactalbumin				0	0	0	?
17. Cabbage		0		0	0	0	1	42. Camel hair				0		0	1
18. Raspberry						0	2	43. Goose feathers	2		?	0		0	?
19. Apple			2	0		0	1	44. Dog hair	0			0	1	0	0
20. Pear	1				0	2	2	45. Goat hair				0	1	0	1
21. Almond	1				0	0	0	46. Horse dander	5			4		3	1
22. Prune				1	0	0	0	47. Flaxseed				0		?	4
23. Pea				0	0	1	0	48. Rabbit hair	2		2	1	1	2	1
24. Kidney bean					1	2	?	49. Sheep wool	1			0		0	0
25. Black-eyed pea					2	3	2								

Figures indicate intensity of positive reactions: ?—plus-minus or borderline: 0—tests done and found negative: blanks indicate test not done.

All tests were done by the scratch technic. Obviously, change from 0 to ? or 1 may have been due to technical variations, but when 2 plus or stronger is balanced by several negatives to the same food this must be interpreted as evidence of a changing degree of sensitization.

While some allergens remained constantly positive (e.g., Nos. 25, 46, 48), others have varied widely (Nos. 1, 3, 13, 19, 29, 32, 36). It is worthy of note that all wheat proteins reacted at one time or another except for glutenin which remained consistently negative. Other foods to which the patient was always negative do not appear in the table.

The table illustrates that in case of doubt or persistent symptoms tests should be repeated because (a) there may be variations due to the technic and (b) actual sensitization may change from time to time.

Sensitization to some allergens persists for years; that to others comes and goes.

CHAPTER XXIX

FOOD GROUPS

It became the custom relatively early in the study of allergy to designate allergenic pollens by their botanical names and to recognize the more or less close relationship between various groups of pollens. Many plants responsible for pollinosis are biologically closely related. The relationship may appear in gross structural characteristics of the plant, in the physical characteristics of the pollen, in some chemical attributes, and finally, in the response to skin testing. Pollens from genetically related plants are likely to cross react, giving positive skin reactions.

Demonstration of crossed sensitization.—If serum from a person allergic to short ragweed is introduced into the skin of a nonallergic recipient, a small zone surrounding the point of introduction becomes passively sensitized to short ragweed allergen. If a test is made at this site with extract of short ragweed pollen, a positive reaction follows. If all of the reagin is used up in this reaction, the passive transfer site will no longer respond positively to short ragweed extract. If not all of the reagin is exhausted in this first reaction, a second positive reaction can be obtained, but as soon as the antibody is used up, the passively sensitized site will no longer react to short ragweed allergen.

If the serum contains at the same time reagins to a totally unrelated allergen such as maple pollen, and if, the ragweed reagin having been exhausted, one now tests with maple extract, the reaction will be positive to the latter. The exhaustion of reagin appears to be specific. If a serum reacting to both giant and short ragweed is used, antibody exhaustion following testing with short ragweed removes the reagin or antibody to giant ragweed. If when positive short ragweed reactions can no longer be obtained, giant ragweed be used as maple was used in the case above, no positive reaction will be observed. Giant and short ragweed are therefore biologically related or possibly identical.

Similar crossed reactions are observed with other pollens, as in some of the commoner grasses. This is so much the case that some investigators believe that in the presence of a positive reaction to the common grasses one may desensitize with timothy extract alone.

To some extent this crossed relationship has also been found to exist among animal allergens. It has been shown, for example, among feathers from different sources. There are some apparently identical proteins in extracts of horse hair, mule hair and zebra hair. It has been stated that the epidermal allergens of cloven hoof animals such as cow and deer are likely to show crossed reactions.*

Genetic classification of foods.—Until 1929, when the writer undertook this portion of his study, no attention had been given in allergy to possible similar crossed relationships among the foods. Until that time only two classifications of foods for skin testing were in use. The first, scarcely a classification at all, consisted merely in an alphabetical listing. The second may be described as the culinary classification, in which foods were grouped into fruits, berries, legumes, nuts, leafy vegetables, starchy vegetables, condiments, cereals,

*Balyeat, Ray M.: Personal communication.

grains, meats, fish, shellfish and dairy foods. This is a utilitarian classification which has its uses, but is based upon only the grossest superficial resemblance of the plants after they have reached the market. Biologically related plants are found scattered through several of the groups.

In collaboration with Dr. Francis H. Wilson, Professor of Botany at the University of Richmond, the botanical classification of the foods customarily eaten was arranged for use in allergic diagnosis. There is nothing new in this classification. It is the classification that has been in use for many years among botanists.

This grouping of edible foods was proposed for several reasons. (1) It is a more rational classification. (2) I had previously gained the impression from observation of food sensitization that if the grouping of foods were properly systematized, we would find evidence of crossed allergic reactions to foods, as had previously been found with pollens. (3) I conceived it as possible that a proper grouping of chemically closely related allergens in a single endermal test might give positive reactions when the individual members were apparently negative. The reactivity of each member of a biologic group might be so slight as to result in false negative reactions. A single test with all members of the group combined might through synergistic effect give a positive group reaction despite the false negative individual reactions. (4) It seemed possible that with foods genetically closely related, one giving a positive skin reaction, the other negative, both might be responsible for symptoms even though the second was skin test negative. If this be true, knowledge of biologic kinship would enable one to circumvent some of the false negative skin reactions by studying the response to ingestion of negative members of a group in which others had been positive. All four of these premises have been found to hold in individual cases. By this I do not mean that if a person reacts positively to one member of a group, all other members, reacting negatively, will necessarily produce symptoms. Many times only the positive reactor causes trouble. Sometimes the positive reactor does not cause trouble, while one of the negative members of the same group does. Here we are dealing with both a false positive and a false negative. An understanding of the biologic relationships facilitates this discovery. Quite frequently one will find that negative members of a positive group do cause trouble.

Food relationships.—A study of Table XXIV brings out some most interesting distributions and relationships. The leafy vegetables are quite scattered, with spinach in group 11, cabbage in 13, parsley 24, lettuce and endive 31. The nuts are found in groups 9, 10, 16, 17 and 19. The fruits are similarly scattered. So also are the condiments.

Walnut and pecan are quite closely related to each other, but not at all to almond, which is a member of the peach family, or to peanut which is one of the legumes. The peanut is indeed scarcely a nut at all, but rather a "goober pea." Peas, beans, peanuts are all much more closely related than are peanuts and walnuts. They are more closely related to clover and alfalfa than to other foods outside their group.

There is surprisingly little difference between the almond and the peach. As it grows on the tree, the almond has a fleshy covering somewhat similar to that of the peach, and the peach has what corresponds to a miniature almond in its stone. They contain a protein, amandine, which is chemically identical in both. (See Fig. 82.)

TABLE XXIV.—BOTANICAL CLASSIFICATION OF THE COMMONER EDIBLE PLANTS

FAMILY	GENUS	SPECIES	COMMON NAME
Monocotyledons			
Graminae	Triticum	sativum	Wheat
	Secale	cereale	Rye
	Hordeum	vulgare	Barley
	Avena	sativa	Oat
	Oryza	sativa	Rice
	Zea	mays	Corn
Palmaceae	Cocos	nucifera	Cocoanut
	Phoenix	dactylifera	Date
Bromeliaceae	Ananus	sativus	Pineapple
Liliaceae	Allium	cepa	Onion
		sativum	English garlic
	Asparagus	officinalis	Asparagus
Musaceae	Musa	sapientum	Banana
Zinziberaceae	Zinziber	officinale	Ginger
Dicotyledons			
Moraceae	Morus	nigra	Black mulberry
	Ficus	carica	Fig
Polygonaceae	Egopyrum	vulgare	Buckwheat
	Pheum	rhaponticum	Rhubarb
Juglandaceae	Juglans	nigra	Black walnut
		regia	English walnut
	Carya	olivaeformis	Pecan
		alba	Hickory
Betulaceae	Corylus	avellana	Hazelnut, filbert
	Castanea	dentata	Chestnut
Chenopodiaceae	Spinacia	oleracea	Spinach
	Beta	vulgaris	Beet
		cycla	Swiss chard
Grossulariaceae	Ribes	vulgare	Currant
		oxyacanthoides	Gooseberry
Cruciferae	Raphanus	sativus	Radish
	Radicula	armoracia	Horseradish
		nasturtium	
		aquatium	Water cress
	Brassica	rapa	Turnip
		campestris	Rutabaga
		alba	White mustard
		nigra	Brown mustard
		oleracea capitata	Cabbage
		oleracea acephala	Kale
		oleracea gemmifera	Brussels sprouts
		oleracea caulo-rapa	Kohlrabi
		oleracea botrytis	Cauliflower (Broccoli)
Rosaceae	Rubus	nigrobaccus	Blackberry
		occidentalis	Black raspberry
		strigosus	Red raspberry
Pomaceae	Fragaria	chiloensis	Strawberry
	Malus	sylvestris	Apple
Drupaceae	Pyrus	communis	Pear
	Prunus	amygdalus	Almond
		domestica	Plum, prune
		avium	Cherry
		armeniaca	Apricot
		persica	Peach
Leguminosae	Pisum	sativum	Pea
	Phaseolus	vulgaris	Kidney bean
		lunatus	Lima bean
	Lens	esculenta	Lentil
	Acharris	hypogaea	Peanut
Rutaceae	Citrus	limonia	Lemon
		grandis	Grapefruit

TABLE XXIV—CONT'D

FAMILY	GENUS	SPECIES	COMMON NAME
Dicotyledons—Continued			
Anacardiaceae	Pistacia	sinensis	Common orange
Vitaceae	Vitis	vera	Pistachio nut
Malvaceae	Gossypium	vinifera	Grape, raisin
		hirsutum or barbadense	Cottonseed
	Hibiscus	esculentus	Okra, gumbo
Sterculiaceae	Theobroma	cacao	Cocoa
Theaceae	Thea	sinensis	Tea
Umbelliferae	Daucus	carota	Carrot
	Pastinaca	sativa	Parsnip
	Apium	petroselinum	Parsley
		graveolens	Celery
Vacciniaceae	Gaylussacia	resinosa	Huckleberry
	Vaccinium	macrocarpon	Cranberry
Oleaceae	Olea	europaea	Olive
Convolvulaceae	Ipomoea	batatas	Sweet potato
Solanaceae	Solanum	tuberosum	Potato
		melongena	Eggplant
	Lycopersicum	esculentum	Tomato
Rubiaceae	Coffea	arabica	Coffee
Cucurbitaceae	Cucurbita	pepo	Pumpkin
		moschata	Winter squash
		maxima	Hubbard squash
	Cucumis	melo	Cantaloupe
		sativus	Cucumber
	Citrullus	vulgaris	Watermelon
Compositae (Chichoriaceae)	Lactuca	sativa	Lettuce
	Tragopogon	porrifolius	Salsify, oyster plant
	Chicorium	intybus	Chicory
		endiva	Endive
Compositae (Asteraceae)	Helianthus	tuberosus	Jerusalem artichoke
	Cynara	scolymus	Artichoke

Cabbage is not at all related to lettuce, but quite closely so to mustard. In this group, 13, one observes great differences in gross appearance among closely related cousins, depending chiefly upon that portion of the plant which becomes especially well developed in the particular species. We might say that mustard represents the seed, cauliflower and broccoli the flower, Brussels sprouts, kale and cabbage the leaf, kohlrabi the stem, and turnip the root of almost one and the same plant (Fig. 78).

While the botanical classification is based upon structural and functional characteristics of the reproductive tissues rather than upon growth morphology, the accompanying figures indicate that there is an easily traced resemblance in the gross appearance of many members of groups. It should be emphasized, however, that this is not the basis for the classification.

Beet and spinach are quite closely related. In the former the root has been especially developed, in the latter the leaf. Swiss chard is the hyperplastic leaf of practically the same plant (Fig. 76).

The superficial resemblance of the leaves of cabbage, kale, broccoli is clearly brought out in the illustrations. The leaf of the tomato or potato is quite different from these, but within the latter group we again find a close resemblance. The fruit of the Irish potato resembles a miniature tomato, scarcely larger than the end of one's thumb. The resemblance of red and green peppers to the tomato is familiar to all. Similarly the cross section of eggplant shows a resemblance.

While Irish potato is quite closely related to tomato, it has no relationship at all to sweet potato, a member of the morning glory family. The leaves and flowers of the sweet potato vine resemble those of the morning glory, Figs. 80 and 86.

Strawberry, raspberry and rose belong in one group. The resemblance in its leaves is striking, particularly when compared with the leaves of foods belonging to other groups, Fig. 80.

The celery group shows an entirely different type of leaf, but characteristic for this group. The same is true of the melon group, Figs. 84 and 88.

Onion, garlic and asparagus are members of the lily family. It is a point of some interest that the two crops for which Bermuda is famous are the onion and the lily. Both belong to the same group. Possibly the Bermuda soil is especially good for this type of crop. Onion and garlic are fleshy stems with overlapping fleshy leaves. Asparagus and chives are also leaves, Fig. 74.

We might carry this classification even farther and say that among alimentary and inhalant allergens, the cereal grains are more closely related to the pollens of the grasses than to other foods; onion, garlic, and asparagus are more closely related to the lily, hyacinth, and tulip; Swiss chard, beet and spinach to the Chenopodiaceae, such as lamb's quarters (*Chenopodium album*); strawberry, blackberry and raspberry to the rose and spirea; the pea-bean family to clover and alfalfa; grape to American ivy and the Virginia creeper; cottonseed and okra to hibiscus, hollyhock, and marshmallow; lettuce, chicory, and endive to dandelion; and artichoke to ragweed and thistle.

Numbers of genera and species.—Our knowledge of systemic botany would lead us to expect more frequent evidence of crossed sensitization in some groups than in others, for the size of the families varies greatly. Thus, in the lily family there are about 300 species. Among the Rosaceae we find 75 genera and 1,200 species. The apple family is relatively small, with 20 genera and 500 species. The pea family is larger, with 325 genera and over 5,000 species. The carrot family, in which crossed reaction is rather frequent, contains about 250 genera and probably 2,000 species. In the potato family there are about 75 genera and 1,750 species. The chicory family, usually placed among the Compositae, contains 70 genera and about 1,500 species. Crossed sensitization with foods and allergenic pollens belonging to the same families is not especially common. When we realize the large number of species in each of the groups, this is understandable.

Early relationships. The evolutionary history of food plants helps us to understand why some are more likely to show crossed reactions than others. Among the Solanaceae, for example, tomato and Irish potato both originated in the region of Chile and Peru and it is possible that they were derived from a common ancestor. Eggplant, on the other hand, although placed in the same botanical group, first appears in history in about 500 or 600 A.D., at which time it is recognized as having existed in Egypt and in China. We should state, however, that potato and tomato have shown infrequent crossed reactions. Only recently have botanists succeeded in hybridizing these two plants.

With the exception of radish and water-cress, the Cruciferae enumerated are supposed by some botanists to have been derived from three species and by others, from one ancestral plant. Their original habitat was eastern Europe and Asia, and they formed a part of the dietary of the ancients before the time of Christ.

Chard was known to the ancients and was described by Aristotle, Theophrastus, Dioscorides, and by Galen. The first record of the beet appears in Europe in the second or third century. The origin of spinach, another member of the *Chenopodiaceae*, is rather more obscure. It appears to have been a new food in Europe in the sixteenth century, but was old in China in the seventh or eighth.

While wheat, rye, and barley may all have been derived from the einkorn of Asia Minor, one would not expect these to show a crossed relationship to Indian corn, which is indigenous to Mexico and North America.

Chemical evidence of relationships.—The clinical findings herein recorded serve to confirm the chemical and immunologic observations that have been made on the proteins of vegetables.

Wells and Osborne have found that “chemically similar proteins from seeds of different genera react anaphylactically in animals sensitized with one another, while chemically dissimilar proteins from the same seed in many cases fail to do so.” They conclude that the specificity of the anaphylaxis reaction depends upon the chemical structure of the protein molecule.

Gortner and Hoffman divide the proteins of the cereal grains into a “wheat group” and a “corn group.” Wells finds the alcohol soluble proteins or prolamines of wheat and rye (gliadin) and of durum, einkorn, emmer, and spelt, all members of the wheat group, to be very closely related, apparently identical according to all immunologic tests applied. These prolamines, however, are not similar to those of the corn group. Hordein of barley is chemically similar to, but not identical with, gliadin of wheat and rye, and immunologically is related to, but distinguishable from these gliadins.

The leguminous seeds contain two globulins, different chemically and immunologically, but the globulins of different legumes may be very similar or identical. The legumins obtained from vetch, lentil, and horse bean appear to be chemically and immunologically identical.

Jones and Wells have demonstrated that the globulin from the seeds of cantaloupe and of cucumber are chemically, crystallographically, and immunologically identical.

Hawk and Bergeim state that the globulin amandin is found both in almond and in peach kernel.

So we find that the problem of biologic food grouping is further complicated by the fact that each food has several different proteins and in varying amounts. Assuming that protein is an allergenic factor in food allergy, the members of a biologic food group that will cross react will, therefore, depend upon their qualitative and quantitative protein content. Minor variations in the protein molecular structure incident to evolutionary development may not prevent crossed sensitization, since there is evidence that only certain portions of the protein molecule may exert a sensitizing action. Finally, we must also recognize that the qualitative and quantitative protein make-up of one portion of a plant may vary from that of another portion of the same plant. When, therefore, we are comparing leafy vegetables with root vegetables, seeds, flowers, fruits, and stems or tubers, we may anticipate some protein variation. McCollum and Simonds recognize this possible variation in protein make-up when they state that “the proteins of the leaves appear to supplement the proteins of the seeds.”

Clinical study. With the collaboration of Sharpe and Dohme and the Mulford Biological Laboratories the writer prepared a series of thirty endoanal

test extracts. With the exception of the grape-okra mixture and certain single foods the solutions all contain biologically related foods. Grape and okra are combined merely for convenience although they are not genetically related. The cereal grains are kept separate for practical reasons. If a person is found allergic to wheat, it becomes important to know to what other cereal grains he may be negative so that wheat substitutes may be recognized.

Advantages.—The writer finds a number of advantages in the application of the biologic grouping to the study of food allergy. Our customary routine consists in preliminary scratch testing with the separate foods. If any food has given a positive reaction, that food or its food group is removed from the endermal test set. Testing is then repeated with the thirty extracts, less those which have been removed. The order in both sets is in accordance with the food grouping. Both may be easily compared. Positive scratch reactions with more than one member of a group show up clearly on the scratch test form, since they are “bunched.” With the use of the endermal groups, the total number of needlings is materially reduced. The patient very much prefers a total of thirty endermal tests, to a much larger number with the individual extracts. When a positive group reaction has been observed, one may test endermally with the individual members of the group. However, this is rarely necessary since, unless a large number of groups have reacted positively, it is easier both for the patient and doctor to advise avoidance of all members of the group. As soon as the patient has been adequately relieved, one after another of the members are again added to the diet, careful observation being made for resultant symptoms.

Illustrative cases. The following cases illustrate the manner in which an understanding of the food groups promotes greater accuracy in interpretation of the skin test.

Food	Reactions	Symptoms	Food	Reactions	Symptoms	Food	Reactions	Symptoms
Wheat			Cabbage			Orange		
Rye			Cauliflower			Grapefruit		
Barley			Mustard			Grape		
Oat			Rosaceae			Okra		
Rice			Blackberry			Cocoa		
Corn			Strawberry			Umbelliferae		
Cocoanut			Raspberry			Parsley		
Pineapple			Pomaceae			Celery		
Liliaceae			Apple	I		Parsnip		
Onion		I	Pear	I		Carrot		
Garlic			Drupaceae			Sweet Potato		
Asparagus			Almond			Solanaceae		
Banana			Cherry	IU		Tomato		
Ginger			Apricot	IU		Potato		
Juglandaceae			Plum	IU		Egg Plant		
Walnut			Peach	IU		Coffee		
Pecan			Leguminosae			Cucurbitaceae		
Chenopodeaceae			Pea			Pumpkin		
Swiss Chard			Lima bean			Squash		
Beet			Kidney bean			Cantaloupe		
Spinach			Lentil			Cucumber		
Cuciferiae			Peanut			Watermelon		
Radish			String bean			Compositae		
Turnip			Butaceae			Lettuce		
			Lemon			Artichoke		

Fig. 54.

A woman complained of indigestion, mucous colitis and urticaria. She had learned from experience that symptoms were produced by cherry, plum, prune, apricot and peaches. Almond caused no trouble. Skin testing with the individual foods showed positive reactions to cherry, apricot and peach and also to almond. Plum was negative. The group reaction was positive.

The false positive almond reaction is explained in a measure at least as being associated with sensitization to other members of the group. Plum was negative and yet plum caused symptoms. That the reaction was a false negative is indicated by the positive reactions to other members of the group. (Fig. 54.)

Apples caused indigestion, while uncooked pear produced angioneurotic edema of the mouth. Cooked pear was tolerated. She gave a positive group reaction, also a positive individual reaction to apple. The pear reaction was negative. Onion gave a borderline individual scratch reaction. The group reaction was negative but trial showed that onion caused indigestion with vomiting. Here the group test failed, was a false negative. One may observe false positive and false negative group reactions as well as individual reactions. Ginger, kidney bean, parsnip, and tomato, all positive, failed to produce symptoms.

Food	Reactions	Symptoms	Food	Reactions	Symptoms	Food	Reactions	Symptoms
Wheat			Cabbage			Orange		
Rye			Cauliflower			Grapefruit		
Barley			Mustard			Grape		
Oat			Rosaceae			Okra		
Rice		U	Blackberry			Cocoa		
Corn			Strawberry			Umbelliferae		
Cocoanut			Raspberry			Parsley		
Pineapple			Pomaceae			Celery		U
Umbelliferae			Apple			Parsnip		
Onion			Pear			Carrot		
Garlic			Drupaceae			Sweet Potato		
Asparagus			Almond			Solonaceae		
Banana			Cherry			Tomato		
Ginger			Apricot			Potato		
Mugiladaceae			Plum			Egg Plant		
Walnut		I	Peach			Coffee		
Pecan			Leguminosae			Cucurbitaceae		
Chenopodeaceae			Pea		U	Pumpkin		
Swiss Chard			Lima bean		U	Squash		
Beet			Kidney bean		U	Cantaloupe		
Spinach			Lentil		U	Cucumber		
Cruciferae			Peanut		U	Watermelon		
Radish			String bean		U	Compositae		
Turnip			Rutaceae			Lettuce		
			Lemon			Artichoke		

Fig. 55.

Food	Reactions	Symptoms	Food	Reactions	Symptoms	Food	Reactions	Symptoms
Wheat			Cabbage			Orange		
Rye			Cauliflower			Grapefruit		
Barley			Mustard			Grape		
Oat			Rosaceae			Okra		
Rice			Blackberry			Cocoa		
Corn			Strawberry			Umbelliferae		
Cocoanut			Raspberry			Parsley		
Pineapple			Pomaceae			Celery		
Umbelliferae			Apple			Parsnip		
Onion			Pear			Carrot		
Garlic			Drupaceae			Sweet Potato		
Asparagus			Almond			Solonaceae		
Banana			Cherry			Tomato		
Ginger			Apricot			Potato		
Mugiladaceae			Plum			Egg Plant		
Walnut			Peach			Coffee		
Pecan			Leguminosae			Cucurbitaceae		
Chenopodeaceae			Pea		U	Pumpkin		
Swiss Chard			Lima bean		U	Squash		
Beet			Kidney bean		U	Cantaloupe		
Spinach			Lentil		U	Cucumber		
Cruciferae			Peanut		U	Watermelon		
Radish			String bean		U	Compositae		
Turnip			Rutaceae			Lettuce		
			Lemon			Artichoke		

Fig. 56.

A patient failed to give any positive individual reactions in the pea-bean group, but the group reaction was positive. The members of the group were found to cause urticaria. Celery and parsnip were only borderline but the group was positive. These two foods caused urticaria. Walnut, pecan and the endermal group were all negative, but later study demonstrated that walnut was responsible for attacks of indigestion. Here were false negative reactions that were not circumvented. (Fig. 55.)

A woman with eczema and indigestion was positive to parsnip which on subsequent trial was found not to produce symptoms (false positive). Celery which had reacted negatively was found on subsequent trial to cause eczema. Carrot which had been only borderline produced indigestion. The group reaction had been positive. In the pea-bean and squash groups

Food	Reactions Symptoms	Food	Reactions Symptoms	Food	Reactions Symptoms
Wheat		Cabbage		Orange	
Rye		Cauliflower		Grapefruit	
Barley		Mustard		Grape	
Oat		Rosaceae		Okra	
Rice		Blackberry		Cocoa	
Corn		Strawberry		Umbelliferae	
Cocconut		Raspberry		Parsley	
Pineapple		Fonacace		Celery	
Liliaceae		Apple		Parsnip	
Onion		Pear		Carrot	
Garlic		Cruciferae		Sweet Potato	
Asparagus		Almond		Solanaceae	
Banana		Cherry		Tomato	
Ginger		Apricot		Potato	
Juglandaceae		Plum		Egg Plant	
Walnut		Peach		Coffee	
Pecan		Leguminosae		Cucurbitaceae	
Chenopodiaceae		Pea		Pumpkin	
Swiss Chard		Lima bean		Squash	
Beet		Kidney bean		Cantaloupe	
Spinach		Lentil		Cucumber	
Cruciferae		Peanut		Watermelon	
Radish		String bean		Compositae	
Turnip		Butterbean		Lettuce	
		Lemon		Artichoke	

Fig. 57.

Food	Reactions Symptoms	Food	Reactions Symptoms	Food	Reactions Symptoms
Wheat		Cabbage		Orange	
Rye		Cauliflower		Grapefruit	
Barley		Mustard		Grape	
Oat		Rosaceae		Okra	
Rice		Blackberry		Cocoa	
Corn		Strawberry		Umbelliferae	
Cocconut		Raspberry		Parsley	
Pineapple		Fonacace		Celery	
Liliaceae		Apple		Parsnip	
Onion		Pear		Carrot	
Garlic		Cruciferae		Sweet Potato	
Asparagus		Almond		Solanaceae	
Banana		Cherry		Tomato	
Ginger		Apricot		Potato	
Juglandaceae		Plum		Egg Plant	
Walnut		Peach		Coffee	
Pecan		Leguminosae		Cucurbitaceae	
Chenopodiaceae		Pea		Pumpkin	
Swiss Chard		Lima bean		Squash	
Beet		Kidney bean		Cantaloupe	
Spinach		Lentil		Cucumber	
Cruciferae		Peanut		Watermelon	
Radish		String bean		Compositae	
Turnip		Butterbean		Lettuce	
		Lemon		Artichoke	

Fig. 58.

individual reactions were all negative but group reactions were positive. Subsequent observation showed peanut and cucumber responsible for indigestion. On the other hand a positive group reaction in the spinach family was found to be of no allergenic significance. (Fig. 56.)

A woman with indigestion gave negative individual and positive group reactions in the melon-squash family, but cantaloupe and cucumber were found on trial to be responsible for symptoms. This is of especial interest in view of the fact that cantaloupe and cucumber contain at least one identical protein, *cucurbitin*. In this chart there also appear a number of false positive group reactions. These were shown to be falsely positive only after subsequent dietary trial. Onion was negative, asparagus borderline, while the group was positive.

Food	Reactions	Symptoms	Food	Reactions	Symptoms	Food	Reactions	Symptoms
Wheat			Cabbage			Orange		
Rye			Cauliflower			Grapefruit		
Barley			Mustard			Grape		
Oat			Rosaceae			Okra		
Rice			Blackberry			Cocoa		
Corn			Strawberry		U	Umbelliferae		
Cocoanut			Raspberry			Parsley		M
Pineapple			Pomaceae			Celery		M
Liliaceae			Apple		M	Parsnip		M
Onion			Pear			Carrot		M
Garlic			Drupaceae			Sweet Potato		
Asparagus			Almond			Solonaceae		
Banana			Cherry			Tomato		
Ginger			Apricot			Potato		
Juglandaceae			Plum			Egg Plant		
Walnut			Peach			Coffee		
Pecan			Leguminosae			Cucurbitaceae		
Chenopodiaceae			Pea		M	Pumpkin		
Swiss Chard		M	Lima bean		M	Squash		
Beet		M	Kidney bean		M	Cantaloupe		
Spinach		M	Lentil			Cucumber		
Cruciferae			Peanut		M	Watermelon		
Radish			String bean		M	Compositae		
Turnip			Rutaceae			Lettuce		
			Lemon			Artichoke		

Fig. 59.

Food	Reactions	Symptoms	Food	Reactions	Symptoms	Food	Reactions	Symptoms
Wheat			Cabbage		I	Orange		
Rye			Cauliflower			Grapefruit		
Barley			Mustard			Grape		
Oat			Rosaceae			Okra		
Rice			Blackberry			Cocoa		
Corn		I	Strawberry			Umbelliferae		
Cocoanut			Raspberry			Parsley		
Pineapple			Pomaceae			Celery		
Liliaceae			Apple			Parsnip		
Onion			Pear			Carrot		
Garlic			Drupaceae			Sweet Potato		
Asparagus			Almond			Solonaceae		
Banana			Cherry			Tomato		
Ginger			Apricot			Potato		
Juglandaceae			Plum			Egg Plant		
Walnut			Peach			Coffee		
Pecan			Leguminosae			Cucurbitaceae		
Chenopodiaceae			Pea			Pumpkin		
Swiss Chard			Lima bean			Squash		
Beet			Kidney bean			Cantaloupe		
Spinach			Lentil			Cucumber		
Cruciferae			Peanut			Watermelon		
Radish			String bean			Compositae		
Turnip			Rutaceae			Lettuce		
			Lemon			Artichoke		

Fig. 60.

Neither of these caused symptoms but garlic belonging in the same group was found to produce indigestion. The citrus fruits were negative both dermally and endermally but subsequent trial showed lemon to be allergenic. (Fig. 57.)

A woman with vasomotor rhinitis was found to experience symptoms only from foods which with the exception of sweet potato had given negative individual reactions. But they had been under suspicion because of positive group reactions or positive individual reactions among other members of the group. In this way the etiologic agents had been traced. (Fig. 58.)

The case of a woman with migraine is of special interest in that among three food groups every one of the constituent foods which she was accustomed to eating caused headache.

It becomes obvious from these illustrative cases that the biologic classification aids in obviating the disadvantage of the false negative reaction. The false positive reactions are still with us. They are illustrated in marked degree in the case of a man with mucous colitis who gave a large number of positive and borderline reactions but had symptoms from only two foods neither of which had shown up on skin testing, Fig. 60. As has been brought out, especially by Rackemann, the positive skin reaction is "an historical landmark," indicating not only trouble at the time, but past trouble, no longer sufficiently active to cause clinical symptoms, and also potential future trouble. This is a distinct disadvantage of the skin test.

Animal food groups. Ellis, in confirming our own observations on the value of the botanical classification, has added a similar classification of the animal foods, again following the principle of homology. He emphasizes that among the animal foods there has been as irrational a classification as far as its application to allergy is concerned as in the culinary classification of vegetables. Thus lobster, shrimp, oyster and scallop are classed under the general heading shellfish. The first of these are as far removed genetically from the last two as are any of the food plants from the ferns. The first two are *arthropods*, while mussels, oysters, scallops, snails, abalone, clams and squid are families of the phylum *mollusca*. Tuft and Blumstein (1940) presented evidence of a common antigenic factor among the members of the Mollusca and Crustacea families. The Crustacean antigen was not related to the Molluscum antigen and neither was related to the members of the true fish family. In 1946 they reported that there is a common antigen among members of the true fish family. There may be great quantitative variation so that testing with multiple fish extracts is warranted except when some one gives a very intense reaction in which event it should be taken as representative of the entire group.

Demonstration of crossed food sensitization by antibody neutralization.—Baldwin and Benedict have given further substantiation to the concept of crossed relationship. A patient reacted to celery, carrot, parsnip and parsley. They incubated his serum with carrot extract. This procedure theoretically fixes the carrot reagin of the serum to the carrot antigen, in a neutralization reaction. This antigen-antibody mixture was then injected into the skin of nonallergic recipients, according to the Prausnitz-Küstner technic. Subsequent testing with carrot extract showed no positive reaction, indicating that the carrot reagin had been neutralized. Similar sensitized sites injected with celery, parsnip and parsley also failed to react. In other words all four reagins had been neutralized by carrot extract. The same results were obtained when the neutralization was carried out with celery extract or with extract of parsnip or parsley. The patient's serum also contained reagin to ragweed. Serum, neutralized with carrot antigen and injected into the skin of a non-allergic, failed to give positive passive transfer to carrot, celery, parsnip or

parsley but did react to ragweed. This would indicate crossed neutralization among the members of the group, with failure of neutralization of an unrelated allergen.

These authors obtained similar responses with serum positive to the apple group; apple, pear and quince. Reagin neutralization with one resulted in neutralization of the reagin for the other two. Similar results were obtained with asparagus and onion of the lily family. With those who reacted both to wheat and rye, crossed neutralization was shown to exist, but was incomplete. After the serum had been neutralized with rye allergen, the Prausnitz-Küstner reaction was negative to rye but it was still one plus to

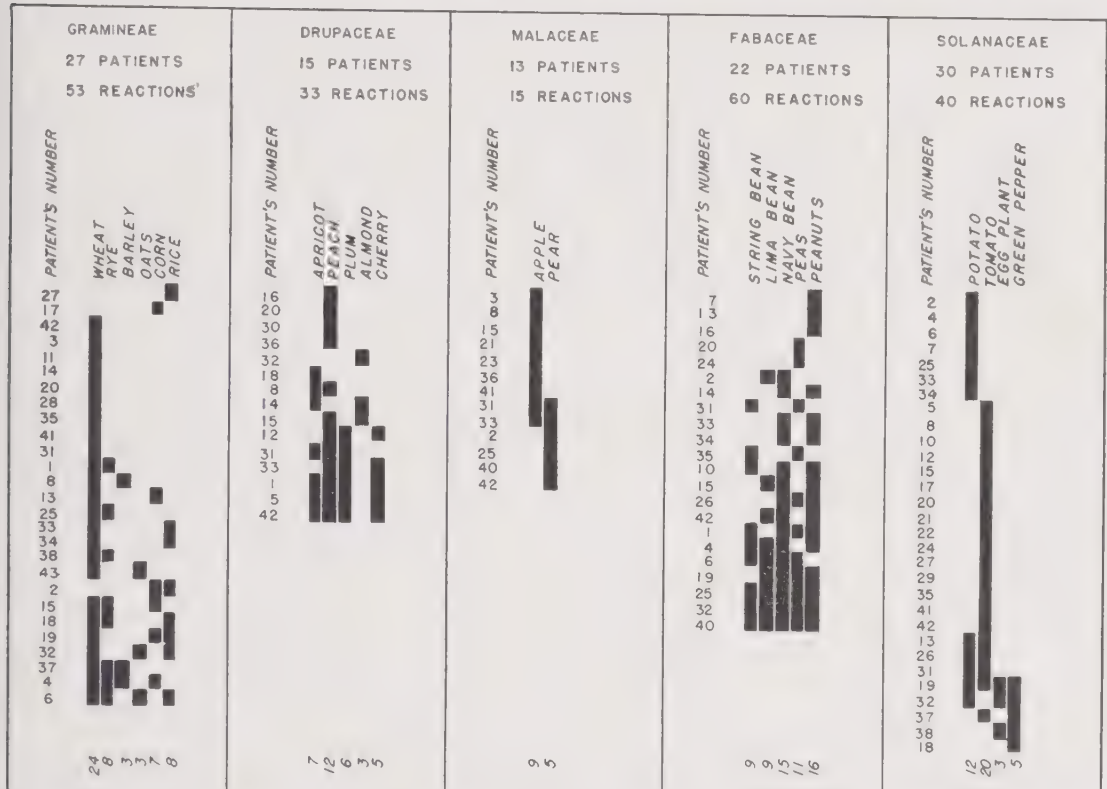


Fig. 61.—Frequency of clinical sensitization to multiple members of biologic food groups. (After Withers.) In some groups such as the pea-bean group, multiple sensitization is more common than in others (apple-pear). Some react only to single members, experiencing no difficulty from others in the same group. Others react to various combinations.

wheat. It had been three plus prior to rye neutralization. The reverse was also true.

Finally as a control they repeated the test, but using allergen extracts from unrelated groups instead of the same group. They used carrot, apple and ragweed. They found that when unrelated allergens were used there was no neutralization except for the one allergen used in the absorption experiment. Thus, with serum containing reagins to carrot, apple and ragweed, absorption of carrot reagin resulted in a negative P-K reaction to carrot, but it was still positive to apple and ragweed. Corresponding specific results were obtained when absorption was carried out with ragweed or apple.

Demonstration by clinical response.—Withers has carried the study one step farther. Forty-three persons, 24 females, 19 males, all proved cases of

food sensitization, cooperated in keeping a careful record of those foods which definitely caused symptoms.

Twenty-two patients were allergic to members of the pea-bean group. Five foods were studied: peanut, navy bean, pea, lima bean and string bean. Only 5 experienced symptoms from but one member of the group, either peas or peanuts. Six were allergic to 2 members, 4 to 3, 4 to 4, and 3 to all 5 members of the group. There was no constant combination, various combinations of positives being observed. Peanuts caused trouble more frequently than the others although navy bean and peas were a close second and third. In this family multiple sensitization appeared to be the rule.

Nineteen experienced allergic symptoms from one or more members of the cucumber family, about half reacting to but one member and half to more than one. The three foods studied were watermelon, cantaloupe and cucumber. Fifteen reacted to watermelon, 10 to cantaloupe and 7 to cucumber. Three patients reacted to all 3 foods; 7 to 2 foods. It is of interest that about 50 per cent of those reacting to watermelon had symptoms following its ingestion only during the autumn pollen season.

In the peach group, among 15 patients, 12 had symptoms from peach, 7 from apricots, 6 from plum, 5 from cherry, and 3 from almond. Three reacted to 4 foods, 6 to only 1. Three reacted to 3 foods; 3 to 2. It will be seen that in this group also there was no constant combination of reactions. Peach was the most frequent offender. Only when sensitization was multiple (3 or 4) did cherry also cause symptoms.

The apple-pear allergies comprised 13 patients. Eleven reacted to only 1 member, either apple or pear. Only 2 experienced symptoms from both. It is especially interesting that more than half of those who had symptoms from apple or pear also had symptoms from peach. These two families are fairly closely related.

Eleven experienced symptoms from one or more of the citrous fruits. Five were allergic to but 1, 4 reacted to all 3 members of the family, orange, lemon and grapefruit, while the remaining 2 reacted respectively to orange and lemon and orange and grapefruit. Multiple sensitization existed in over half.

Among 11 who reacted to the lily family 8 had symptoms from 1 food only (6 from onions and 2 from asparagus) while 3 reacted to both. One of these also had symptoms from garlic.

In the walnut-pecan group, 9 had symptoms. Six reacted to 2 or more foods, the remainder to only 1 member of the group. English walnut and black walnut sensitizations were often found in the same patient.

Seven reacted to strawberry, 1 to strawberry, blackberry and red and black raspberry and another to red raspberry and strawberry. In the mustard-cabbage group Withers found similar frequent crossed reactions between turnip, cabbage, cauliflower and Brussels sprouts, especially the three latter.

Crossed sensitization appeared even in the buckwheat family. There were 5 patients, all of whom reacted to buckwheat and 3 of whom had symptoms from rhubarb.

In the beet family, patients were tested with beet and spinach. Four reacted to spinach and 2 of them also had symptoms from beet. Three of the 4 who were allergic to spinach also had symptoms from buckwheat, a member of a reasonably closely related family.

In the potato family, evidence of crossed reaction was not as pronounced. Thirty had symptoms from one or another of this group. This comprised the largest group representation. Allergy to tomato was commonest, there being 20 who experienced symptoms. Four of the tomato allergies were also sensitized to potato. Two of the 3 reacting to eggplant also reacted to Irish potato and green pepper; 1 had symptoms from all 4 members of the group including tomato.

Twenty-seven reacted to 1 or more of cereal grains. Wheat was the commonest offender, with 24; rye next with 8; while 3 each reacted to barley and oats, 5 to corn, and 8 to rice. Ten reacted to only 1 food. Four reacted to 4 of the 6 members of the family. Multiple sensitivity in this group, as in the tomato-potato group, was not as frequent as in the other families mentioned. Ten reacted to 1 cereal, 10 to 2, 5 to 3 and only 2 patients reacted to 4.

Discussion

Summarizing the evidence concerning the allergic significance of biologic food groups, we have found evidence of crossed relationship and have demonstrated its value, especially in detecting false negative reactors; Baldwin and Benedict have presented experimental evidence of a chemical or immunologic crossed relationship; and Withers has confirmed the clinical evidence by studies on a series of patients with known sensitization. In addition, Ellis has called attention to the importance of similar grouping of animal foods, especially seafoods.

Although there has been increased recognition of the importance of biologic relationships there has been less use of "group tests." The mixing results in lower concentration of each of the components than when used separately. It is possible to secure negative reaction to the group while some one component may react when tested separately. The converse may also occur.

CHAPTER XXX

TRIAL DIETS

The diagnostic study of the patient with food allergy has, up to this point, been carried through the stages of discussion with the patient, skin testing by the dermal and endermal method, with due attention to the biologic groupings, and a second discussion with the patient of the results of testing. He is now ready to be placed upon a therapeutic dietary program, but the study is not yet complete, since in all probability all false negative reactors have not yet been discovered and there are doubtless a number of false positive reactions.

False positive reactions. Some false positive reactions are probably due to irritants in the extract and are nonspecific. This is especially so with endermal testing. Other positives indicate past or future trouble. However, one cannot say offhand which positive reactions are true and which are false as far as present symptoms are concerned. In a given case, all positives may be true ones, all may be false, or both may be present. In my experience and with the technic which we employ, approximately 50 per cent of the positive reactions observed are true positives, indicating foods of present allergenic importance, while the other half represents foods which may safely be eaten. However, since there is no way in which one may tell which are true and which false, the logical procedure at this stage is to have the patient avoid all positively reacting foods, unless the list be too great. As soon as symptoms are adequately relieved, one after another of the prohibited foods may be added to the diet. In this way one will gradually discover those which cause symptoms and those which do not. The method of food addition will be described later.

What foods to avoid. Where positive reactions occur to individual members of food groups, one may follow either of two procedures. If the dietary restriction is not too great, that is, if there have not been too many positive reactions, one may direct the patient to avoid all members of that group, no matter whether the others were positive or negative. If, on the other hand, this would cause too radical restriction with resultant dietary deficiency, the patient may be advised to avoid the positive reactors and watch carefully the effect of ingestion of the negative members of the group. Here it is a matter of good judgment and an adjustment of the restrictions according to the severity of the patient's symptoms, his general physical condition, etc. One can always prohibit more foods at a later date if necessary, although I personally prefer, whenever possible, to make the restrictions more radical at the beginning and gradually add foods rather than to subject the patient to the psychic trauma of watching his diet become progressively more restricted.

We have stated that the prescription of a diet based upon the observations up to this point does not complete the diagnostic study of food allergy. At this point treatment begins but the diet is in every sense a trial diet, to be modified subsequently depending upon the progress of the case. This is an elimination diet similar to those recommended by Rowe but differing in the fact that it is completely individualized for the patient. Like the elimina-

tion diet, the individualized trial diet need not be a balanced diet, with proper quanta of protein, fat, carbohydrates, vitamins and salts, provided both the patient and the physician realize that it is temporary, designed to relieve symptoms in as short a time as possible, a diet to which additions must be made within a period of from two to four weeks, if nutritional elements are inadequate.

Attention to known idiosyncrasies.—In prescribing, the physician should take cognizance of the patient's previous experience with food idiosyncrasies as brought out in the history of the present illness and as shown on the form on page 151. He should compare both, especially the latter, with the results of skin testing. Not infrequently this shows crossed reaction in food groups. For example, a patient may have experienced urticaria from peaches and yet the skin test to peach may have been negative, but that to apricot positive. The patient's own past experiences should be considered when formulating the dietary prescription, even though the skin reactions did not correspond. Very frequently they do correspond and when this occurs the positive skin reaction may be looked upon as confirmation of the patient's own experience.

Methods of prescribing the diet.—The trial diet may be presented to the patient in several ways. The simplest, although not always the most satisfactory, is in a negative form—merely a list of those foods which must be avoided. The prohibitions must be explicit. Many foods appear in various guises in the menu and the patient must be warned against them. This applies especially to wheat, egg, milk, chocolate, oils and some of the condiments. Unless warned, a patient may carefully avoid pork as directed, while continuing to eat ham or bacon, or foods cooked with "hog lard."

TABLE XXV.—SPECIAL DIET PRESCRIPTION

Name _____	Date _____
<i>You should eat the following foods:</i>	<i>You must abstain from:</i>
Fruits:	Fruits:
Cereals:	Cereals:
Breads:	Breads:
Soups:	Soups:
Green vegetables:	Green vegetables:
Starchy vegetables:	Starchy vegetables:
Meats and fowl:	Meats and fowl:
Sea foods:	Sea foods:
Dairy products:	Dairy products:
Salads:	Salads:
Desserts:	Desserts:
Condiments:	Condiments:
Sauces:	Sauces:
Nuts:	Nuts:
Beverages:	Beverages:
<i>General directions:</i>	
This diet is prescribed for-----weeks and must not be continued longer without further consultation. Please bring this list with you at each visit.	

Such a list of foods to be avoided is satisfactory when the list is not too long or complicated. The longer it is, the more the patient will become convinced that there is nothing left for him to eat. In such a case it is desirable to, at the same time, furnish a list of those foods which *may* be eaten. The simplest procedure is to provide a list of all foods generally available such as the form on page 146 on which articles to be avoided have been crossed out. Foods not crossed out may be eaten. The same purpose is accomplished by

providing the patient with copies of the skin test sheets. This has an advantage in that it enables him to compare symptoms following the ingestion of suspected foods, with the skin tests. In this way it is sometimes discovered that borderline reactors are truly allergenic. A disadvantage is that an over-conscientious patient may feel that any marks after a food indicate trouble and may of his own accord restrict his diet more than is necessary. If the patient is supplied with copies of the tests he should understand that he is to avoid only those foods which have been specifically designated, even though others on the list are recorded positive or borderline.

If one prefers one may provide the patient with very elaborate menus listing a selection of foods for the three meals, special recipes, etc.

Formal Dietary Instructions

Diet for Mr. P—

Wheat-free and rye-free, with avoidance of peas, peanut, lentil, lima, kidney and string beans.

Breakfast

1. Fruits: All kinds.
2. Cereals:

Cornflakes	Puffed Rice
Post Toasties	Oatmeal
Rice Flakes	Hominy grits
Rice Krispies	
3. Eggs: Scrambled, soft or hard cooked, omelets, coddled, baked or poached. Do not use wheat in preparations such as bread crumbs, or cream sauce which contain wheat flour.
4. Breads: Corn bread, corn muffins.
5. Beverages: Those made without wheat and rye. See recipes on "Special Sheet."
6. Butter, cream and milk. Coffee, tea, Baker's cocoa and chocolate, and fruit juices.
7. Sugars:

Brown, granulated, maple.
Home made jellies, jams, preserves.
 (Those purchased in stores frequently contain wheat products.)

Lunch or Dinner

1. Soups:

Home made cream soups, except pea and bean.
Home made meat soups and broth.
Home made vegetable soup, but omit peas and beans.
2. Meats: All meats may be eaten if they are not prepared with wheat or rye products. Ready prepared meats such as hamburger, meat loaf and sausage frequently contain wheat products.
3. Gravies: Only those thickened with cornstarch.
4. Vegetables:

Beets	Onion	Lettuce
Kale	Carrots	Sauerkraut
Okra	Asparagus	Spinach
Cabbage	Celery	Peppers
Cauliflower	Radish	Cucumbers
Brussels sprouts	Artichokes	Parsnips
Broccoli	Corn	Salsify
Turnips	Leeks	Eggplant
Rutabaga	Mustard greens	Irish potato
Squash	Tomato	Sweet potato
5. Breads: Corn bread, corn muffins and those made without wheat and rye.

6. Salads:

Made from fruits or vegetables listed.

Do not use any mayonnaise or salad dressing except those made at home.

7. Desserts:

Use no wheat or rye products in preparation

Fruit jello or gelatin

Home made ices, or ice creams

Cornstarch pudding

Oatmeal cookies

Charlotte russe

Baked custard

Fruit cup

Spanish cream

Bavarian cream

8. Beverages:

Coffee, tea, fruit juices.

9. Butter, cream and milk.

Miscellaneous

1. Pickles

2. Condiments:

Salt, pepper, sage, cinnamon, cloves, garlic, ginger, horse-radish, mint, mustard, nutmeg, paprika, pimento, and vanilla.

3. Nuts:

All except peanuts.

4. Olives

5. Candies:

Home made candies.

6. Popcorn

7. Fish:

All except bass, salmon, sole and herring.

Note:

The following should be avoided since they may contain wheat or rye.

Postum

Yeast

Ovaltine

Malt products

Ry-Krisp

Macaroni

Pretzels

Noodles

Zwieback

Spaghetti

Vermicelli

Special recipes: See special recipes, attached.

There are conditions in which skin tests are notoriously fallible, such as eczemas and urticarias; there are patients whose skin tests are all negative in the face of a clinical allergy; there are those whose physical condition may make skin testing inadvisable, and there are those who show no clinical improvement after removing from the diet those foods which showed skin reactions. These persons may be placed on restricted diets and much valuable information obtained.

For several years we have used a diet which is quite different from those usually used, and has been of great help. It was first proposed by Andressen and has been modified by us. It is shown in the form in which we have used it.

Diet List

Bread (wheat) plain or toasted

Whole wheat bread

Biscuit

Rolls

Crackers, plain or graham

Wheat cereal (Bran, Cream of Wheat, Grape Nuts,

Puffed Wheat, Ralston, Shredded

Wheat, Wheaties)

Waffles or griddle cakes

Postum

Milk, sweet, butter milk, cream, butter, cheese

Malted milk

Eggs

Macaroni or spaghetti with or without cheese

Vanilla ice cream

Diet List—Cont'd

Plain pound cake
Vanilla wafers
Angelfood cake
Beef steak, roast, liver, tongue, sweetbreads, veal
Potato, mashed, fried, baked, boiled, au gratin, O'Brien
Orange, juice, sherbet, marmalade
Salt
Sugar
You may use any amount of these and as often
as you wish. Do not use even the least amount
of anything not listed above.

It will be noted that this diet contains only wheat, milk, egg, beef, potato, orange, sugar, and salt. These give the patient an adequate caloric intake. The basis on which this diet is used is that it consists of foods which are common causes of allergy and, if the patient is sensitive to any food, it is quite likely that he is sensitive to one of these. If so, he will promptly have an aggravation of his symptoms. If his is not sensitive to any of these but to some food not included in the diet, he should be definitely better or even well by the end of a week. If symptoms become increased within forty-eight hours after beginning the diet, the patient is placed on a general diet with the exception of some one of those in the diet, and kept on this for five or six days. If he does not improve markedly in this time, the food which had been restricted is replaced in the diet and another of the original group is removed. In this manner one may go through the small list of foods in the diet and determine which may be the cause of the symptoms.

If the patient does not get worse within forty-eight hours, it is assumed that he is not sensitive to any food in the diet, and is told to use the diet for a full week. If, at the end of this period, he is well or much improved, one food is added at a time, allowing three days for testing each added food during which time the added food is to be eaten in generous amounts. In this way one may frequently determine the food causing the allergic manifestations when skin tests are not advisable or the reactions are not dependable.

This method has a definite advantage over the usual form of elimination diet in that it may precipitate or aggravate an attack and thus show the patient's sensitivity. When attacks of asthma, for example, are widely separated, it is not very satisfactory to place a patient on a highly restricted diet and keep him on it for several weeks waiting to see whether he may have an attack, as is necessary if the attacks are usually weeks apart.

The objection may be raised that patients are frequently sensitive to more than one food. The answer is that though this may be true, it is remarkable how often the avoidance of one food is all that is necessary to secure relief. It is not offered as an infallible method of determining food sensitivity, but it has proved of great value in our hands.

CHAPTER XXXI

THE FOOD DIARY

False negatives.—As we have seen, skin testing provides much of the desired knowledge but at the same time introduces a relatively large amount of fallacious information. The skin test having been completed, one must realize that some of the positive reactions are false while some of the negatives are truly allergenic foods. If all positive foods are eliminated, more than are actually required will be prohibited. Some of the negatively reacting foods are true allergenic excitants and will be left in the diet. An understanding of biologic relationships enables us to recognize some of the false negative reacting foods.

These facts being borne in mind the patient is placed on his trial diet as described in the preceding chapter. Even now the study is not completed since the results of food ingestion will provide information concerning false positives and false negatives.

The food diary.—The principle of the food diary is simple. The patient records all substances ingested each day including foods, drugs, laxatives, alcoholic and nonalcoholic beverages and, indeed, everything that passes the lips, even including chewing gum. Those days on which symptoms occur are appropriately indicated. After the diary has been kept for four or five weeks, a period sufficiently long to include two or more allergic episodes such as migraine, angioneurotic edema, asthma, etc., the physician analyzes the diet in an effort to discover foods which were eaten only on the days or just preceding the days on which symptoms appeared. These foods are then designated as suspicious.

Chief value when symptoms are intermittent.—Obviously, the diary should be especially serviceable when symptoms are intermittent and theoretically of no value when symptoms occur every day. As a matter of fact the diary is to be kept even though symptoms have been occurring each day, because as the patient improves under the preliminary therapeutic program, there develop periods of several days to a week or longer during which he no longer has symptoms. When this occurs, a new trial diet may be formulated consisting of only those foods which have been eaten during the quiescent period. Naturally, those eaten only during the last 24 or 48 hours of the quiescent period are not included, since they may have been provocative agents of the return of symptoms. This new trial diet consisting only of foods eaten during the time when the patient was symptom free should result in permanent relief of symptoms, provided allergy to foods alone is responsible for the symptom complex. Unfortunately this proviso does not hold in many cases. But when it does, when the patient is allergic to foods only, the procedure provides a quick, short cut to relief. Subsequent food additions are made by the escalator method to be described, Figs. 63 and 64.

Method of recording.—It is essential that the patient keep his diary absolutely accurately, since any error will invalidate the analysis. He should therefore bring it in for check-over at the end of the first week although, as a rule, little information can be obtained from its analysis after this short in-

A simple method for the analysis of the food diary, particularly Diary I, is as follows: Determine the days with symptoms from Diary I. Find the corresponding day on Diary II. Draw a vertical red line through the length of the diary for that day. If symptoms occurred chiefly around the middle of the day or throughout the day the red line is placed in the middle of the vertical column. If they occurred early in the day it is moved to the left, if late, to the right. If symptoms occurred before breakfast the red line appears covering the black line separating this day from the preceding one. If symp-

Food	S	M	T	W	T	F	S	S	M	T	W	T	F	S	S	M	T	W	T	F	S	S	M	T	W	T	F	S
Milk				X																								
Vanilla				X																								
Beef				X	X	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Potato				X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Apple sauce				X				X																				
Spinach				X		X							X								X							
Oat meal				X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Coffee				X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Thyroid extract				X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Raw apple				X				X	X	X	X	X	X								X	X	X		X			X
Hominy				X																								
Beets				X									X								X	X			X	X		
Cabbage				X									X												X	X		
Corn pone				X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Veal liver				X									X	X	X						X							
Ry Krisp				X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Cinnamon				X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Sugar				X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Salt				X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Fondant candy				X	X	X	X																					
<u>Dates</u>						X																X	X			X	X	X
Pecans					X			X	X	X	X			X	X	X												
Olives					X																							
Banana					X								X	X	X	X	X		X	X	X	X	X	X	X	X	X	X
Snaps					X																X							
Grapefruit					X																	X						
Corn flakes					X																				X			
Syrup					X																				X			
Chicken					X	X			X	X	X			X	X							X	X					
Green peas					X	X			X	X	X		X	X	X							X						
Rice					X				X					X									X					
Corn					X																							
Raw carrots					X																							
Pineapple					X				X							X												
Jello lemon					X																							
Lettuce					X	X																X	X	X	X	X		
Lamb chop					X	X																X						
Asparagus					X	X																X		X				
Tomato					X																		X		X	X	X	X
Fruit jelly					X				X																			
<u>Canned peaches</u>					X				X	X																	X	
Crab meat					X				X																			
Fish spot					X				X																			
Butter					X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Butter beans					X				X					X								X					X	
<u>Turnip salad</u>					X				X																			X
<u>Orange juice</u>					X				X																			X
<u>Sweetbreads</u>					X				X																	X		X

Fig. 63.—Illustrative food diary. With daily symptoms, as during the first two weeks of this diary, nothing can be determined concerning possible allergenic foods. However, the initial program of dietary restrictions, inhalant avoidance, and inhalant desensitization improved symptoms to such an extent that in the last three weeks of the diary they became intermittent, thus making diary analysis possible. Suspected foods are dates, canned peaches, turnip salad, sweetbreads. It should be borne in mind constantly that symptoms may be due to excitants other than foods.

toms occurred after the evening meal the red line overlaps the black line to the right. A vertical red line is drawn for every day with symptoms shown on Diary I.

If the line is at the left margin for the day, and if foods are playing a part, the cause must be sought for, not in those foods eaten on that day, subsequent to the onset of symptoms, but among the foods of the preceding day.

Food	S	M	T	W	T	F	S	S	M	T	W	T	F	S	S	M	T	W	T	F	S	S	M	T	W	T	F	S
Orange juice	X	X	X	X	X	X	X																					
Ham	X	X	X	X	X	X	X							X													X	X
Toast	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Coffee	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Orange marmalade	X	X	X	X	X	X	X																					
Calcium lactate	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Green peas	X	X	X	X	X	X	X																					
Tangerine	X	X	X	X	X	X	X																					
Chicken	X	X	X	X	X	X	X																					
Gravy	X	X	X	X	X	X	X																					
Grape jelly	X	X	X	X	X	X	X																					
Roll	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Butter	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Brandied peach	X	X	X	X	X	X	X																					
Grapefruit	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Bacon	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Eggs	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Benzedrine In-	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Pickles	X	X	X	X	X	X	X																					
Candy	X	X	X	X	X	X	X																					
Fruit punch	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Steak	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Spinach	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Carrots	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Saraka	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Pear	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Fish roe	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Ginger ale	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Soup	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Crackers	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Chewing gum	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Pineapple	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Lettuce	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Vercolate	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Coca cola	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Apple salad	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Plum pudding	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Peralga	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Beets	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Lamb	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Crab flakes	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X						

Fig. 61. Illustrative food diary. Symptoms are nearly of daily occurrence, but there is a period of one week's freedom. An individualized elimination diet, for temporary use only, may now be drawn up to include nothing but foods eaten during the interval of freedom. Those eaten only during the last 24 or 48 hours are better avoided since they may have been responsible for return of symptoms. Those eaten in the last 24 or 48 hours which were also eaten earlier in the period, without symptoms, may be employed. If, on this diet, symptoms persist, it may be assumed that they are due to causes other than foods.

Interpretation.—Ideally, one should be able, when symptoms are intermittent, to study Diary I with its vertical red lines and promptly observe certain foods recorded as eaten only within the 24 to 48 hours preceding onset of symptoms, not at any other time, and which may therefore be looked upon as presumptive causes of attacks. Very occasionally this does occur. Unfortunately, much more often, the analysis is decidedly more complicated.

It is true that the very strongly allergic individual often has symptoms following each and every contact with the excitant. Such a person also usually gives positive objective evidence, as in the skin reaction. As a consequence, such foods have as a rule already been eliminated. The function of the Food Diary is to enable us to discover the less highly allergenic foods, those to which the patient is more mildly sensitized and which have failed to give positive objective evidence. These foods do not as a rule cause symptoms following each contact or exposure. One may be definitely though mildly allergic, let us say, to shrimp, chocolate and strawberry. Each of these foods is noted for its allergenic capacity. But in the particular case under consideration sensitization is low-grade. Such a person may eat these foods at times with impunity, while at other times their ingestion is followed by symptoms. Or it may be that symptoms occur only after ingestion of two or more at the same time, their activity being in a measure synergistic.

A truly allergenic food may then appear on the diary at the proper interval prior to attacks but it may also appear at other times when the patient is symptom free.

When a patient is reasonably highly allergic to a given food, symptoms become manifest within a relatively short period. The interval may vary from a few minutes to a few hours or even as long as 24 hours. But it may be longer. I know of one woman who develops migraine regularly 36 hours after eating chocolate. Therefore one must take cognizance of all foods eaten within 48 hours prior to symptoms.

Cumulative build ups.—Furthermore, the effect may be cumulative. A single ingestion is tolerated. Possibly ingestion for two or even three successive days gives rise to no symptoms. But if the same mildly allergenic food is eaten every day for four or five days or a week or two, it gradually causes symptoms, which then persist as long as ingestion is continued. Therefore one must also watch for foods which have been ingested for several days prior to flare-up. These might be termed "build up" foods.

Examples of such "build-ups" are not easily found in the analysis of the Food Diary but are very easily brought out in those cases where the patient, having avoided an allergenic food for some time, starts its ingestion again. As an example, a woman with migraine was found positive to egg. After three years of avoidance she was again tested and found negative. She therefore added egg to her diet, eating it practically daily. One month later symptoms returned. She omitted egg, with relief from symptoms. Later, the skin reaction was found again positive. In this case the build up required a month. Such a case, the egg sensitization being unknown, would be difficult to analyze with the diary. Here, others of the methods described must be employed. Fortunately, at the time of first examination the patient has usually been eating the build-up food pretty continuously. As a consequence skin test is likely to be positive. In my experience the build-up may require any

Food	S	M	T	W	T	F	S	S	M	T	W	T	F	S	S	M	T	W	T	F	S	S	M	T	W	T	F	S
Egg, scrambled	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Grits	X	X	X	X																								
Pineapple juice	X	X	X	X	X		X		X	X													X		X	X	X	
Kaffee Hag	X	X	X	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Sugar	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Fried chicken	X						X	X					X	X								X		X				
Garden peas	X		X	X	X		X		X	X			X	X								X		X				
Squash	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Corn bread	X	X	X																									
Pineapple	X	X	X	X					X	X	X				X	X	X	X	X	X	X	X			X	X	X	
Lettuce	X	X	X	X	X	X	X	X	X	X	X			X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Asparagus	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Mayonnaise	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Green beans	X	X	X	X	X		X	X					X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Broiled steak	X	X					X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Banana	X	X	X				X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Grape juice	X																					X						
Lima beans		X	X				X	X																				
Roast beef		X	X												X	X	X					X					X	
Cherries		X	X																									
Bar Nut Candy		X	X				X			X											X							
Coffee			X	X																	X	X				X		
Fried apples			X	X			X	X						X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Tea (iced)			X	X																	X							
Sweet potatoes			X	X			X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Beef liver			X																									
Stewed prunes			X																									
Barley bread			X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Pears			X	X										X														
Bar Walnut Candy			X				X			X																		
Veal liver			X																									
Figs, canned			X	X	X																X	X	X	X		X	X	
Cabbage			X							X	X																	
P.K.Chewing Gum			X							X	X	X	X								X		X	X	X	X	X	
Brown sugar fudge			X																		X		X		X			
Fresh pears																					X		X		X			
Fresh peaches							X							X														
Yellow pears									X																			
Buckwheat cakes									X																			
Maple syrup									X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Butter									X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Stew beef									X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Fish (trout)									X					X														
Caramel Candy									X																			
Honey									X																			
Buckwheat bread									X																			
Slaw									X	X					X		X	X	X						X	X	X	
Bar Pecan Candy									X						X		X	X							X		X	
Beef brains														X	X										X		X	
Salmon														X														
Okra																												
Field peas																												
Frozen pineapple and egg																												
Spinach																												
Dried beef																												
Soft boiled egg																												
Stewed chicken																												
Canned peaches																												

Fig. 65.—Illustrative food diary. The patient had been doing nicely, but as additional foods were added to the basic diet, symptoms recurred. One must search not only for the dietary foods eaten just prior to attacks, but also for cumulative effect from added foods eaten daily. In the above case fried apples, veal liver, buckwheat cakes, maple syrup, buckwheat bread come particularly under suspicion. With a fairly regular periodicity as occurs in this case, one should bear in mind the possibility of overdose reaction to semiweekly injections of desensitizing extracts if such are being given. Other nonfood factors may be playing a part.

interval from two days to a month. As an arbitrary limit, we have found that diary study for a four- to seven-day build-up is usually sufficient for the recognition of most presumptive foods in this category.

Multiple foods and multiple responses.—If but one food were involved the analysis of the food diary would be simplicity itself. However, food allergy is almost invariably multiple, especially after it has existed for some time, and the analysis of the diary usually shows several suspicious foods, one or more of which may be truly allergenic. A food responsible for one attack, as indicated by the red vertical line, may not be the same food causing a later attack. This fact further increases the difficulties of precise analysis.

The patient may have, not one allergic symptom, but two or several, all of which may be due to food allergy. All symptoms may be caused by the same food, or certain symptoms may be caused by one food and others by entirely different foods. This adds to the difficulty of diary analysis. At times the difficulties of the study of multiple symptomatology are obviated in part at least by having the patient fill out several duplicate copies of Food Diary II, one for each of the allergic symptoms. The red symptom lines on each of the No. II Diaries will differ, depending upon the complaint. Analyses are made independently, according to symptoms. If there are only two symptoms, the analysis may be made on a single No. II sheet with two different colored lines. With three or more symptoms a single chart usually becomes too involved.

Associated allergic reactions. Finally, symptoms may be due not only to foods but also to inhalants, contact factors, emotional states and non-specific excitants. From the Diary a food may be selected as suspicious when as a matter of fact the true excitant may have been some inhaled substance. A patient may be placed on a second trial diet based on foods eaten during free intervals as shown in the Diary. While on this apparently nonallergenic diet he may have symptoms due to inhalants. In such a case it is not safe to assume without further study that foods have nothing to do with the symptomatology. Possibly truly allergenic foods were eliminated. At this stage it would be erroneous to put the patient back on a general diet, and concentrate on study of the inhalant allergy. He should be maintained for a time at least on the nonallergic diet while inhalant and other studies are progressing. A return to allergenic foods during the effort to eradicate inhalant factors may cause return of symptoms and ultimate failure of relief.

The analysis of the Food Diary is beset with many difficulties none of which are insurmountable. A very real advantage of the method consists in the fact that it provides the physician with an accurate record of this portion of the patient's daily routine. In spite of the difficulties enumerated, the Diary often provides the needed information for relieving the patient. It is a method the effectiveness of which improves greatly with experience. The writer has found in the course of several years of instruction of men in the study of allergy that an average of six months of Diary analysis is required before the analyst becomes proficient with the method. One may not anticipate startlingly effective results from the beginning.

Program after analysis. Let us assume that the Diary has been kept for a month or longer and that certain foods have been designated by the analyst as suspicious. The patient may now avoid all suspicious foods. This is possible if his original restrictions have not been numerous. Otherwise there is real danger of too radical restriction. The patient may continue eating the

suspicious foods, meanwhile studying any possible symptoms following their reingestion. If this is done he is cautioned to add only one suspected food to his basic diet at a time and, preferably, to eat it for several days in succession, to provide a build-up. As a rule from four to seven days suffice. If there has been no return of symptoms the second suspected food is tried in the same manner. If symptoms have returned, the basic diet is followed until the patient is again symptom free, following which he tries the second suspected food.

Directions for Use of Food Diary No. I

Read Very Carefully

Write down anything you eat or drink (except water) in the proper square for each day. This includes not only foods but medicine, laxatives, chewing gum, etc. It must also include substances taken between meals. Write your summary and remarks or interesting observations for the week, below, and, if necessary on back of sheet.

No. 1—Breakfast—In the proper space write down everything that you eat and drink (except water) for each day during the week.

No. 2—Food between meals—If anything is eaten or drunk (except water) between breakfast and lunch, designate in this space.

No. 3—Medicine—Any medicine taken between breakfast and lunch, even immediately prior to lunch, should be noted here.

No. 4—Lunch—Write in all foods and drinks taken for lunch each day of the week just as explained for breakfast.

No. 5—Includes foods or drinks taken between lunch and dinner. This of course includes beverages before dinner.

No. 6—Includes medicine taken between lunch and dinner.

No. 7—Food and drinks taken for dinner.

No. 8—Food or drinks taken after dinner.

No. 9—Includes not only medicine taken between dinner and bedtime, but before breakfast, also. However, if medicine is taken just before breakfast, this should be mentioned on bottom of page or back of sheet.

In the weather and temperature spaces indicate such events as rain or snow and at what time during the day. Mention also the approximate degree of temperature.

Miscellaneous Events includes all activities other than daily routine, such as attending movies, church, etc. Also any special events which are related to symptoms.

In the treatment spaces (bottom row), indicate on what day or days you received your injection of extract or vaccine.

If alcohol is taken, always state what kind: as Rye, Scotch, Martini, etc.

In case you have a symptom for which there is no Key, devise your own key, being sure to explain what it means: as G.P.—gas pains, H.B.—heart burn, etc.

The Vaughan-Graham Clinic, Richmond, Virginia.

Directions for Food Diary II

(Illustrated in Figs. 62-65)

Record all foods eaten, in the left-hand column. On this list it is not necessary to separate the foods according to meals. The letter across the top of the page refers to the day of the week. Just above each letter write in the day of the month. Start the record on Sunday. The first day, write down all the foods and check them all in the proper column. On the second day, check all the foods previously listed, which you happened to eat on the second day. Any new foods eaten will be added in the left-hand column and these will all be checked for the second day. On the third day, check all foods previously listed which are eaten also that day and add any new foods, checking them also. Continue in this way through the five-week period. Make duplicates of this sheet, one for each of the different symptoms you have recorded on "Food Diary" sheet.

Under any circumstance the patient continues his Food Diary, starting a new set of forms. He will continue to keep the Diary indefinitely, until the food factors have been completely worked out. Not infrequently symptoms are too frequent during the first month for satisfactory analysis but during the second or third month, when other factors have been more adequately controlled, symptoms are infrequent and the Diary is easily analyzed.

under special suspicion. Following completion of the Diary, suspected foods may be tested objectively with the leukopenic index. If the index is negative the patient may continue to eat the suspected food. If positive, especially after a build-up, he will avoid it.

Assuming that during the period of the Diary the patient has been adequately relieved, we may conclude that as far as foods are concerned excitants have been removed and no false negative reactors have been overlooked. The possibility remains that because of season or for some other reason,

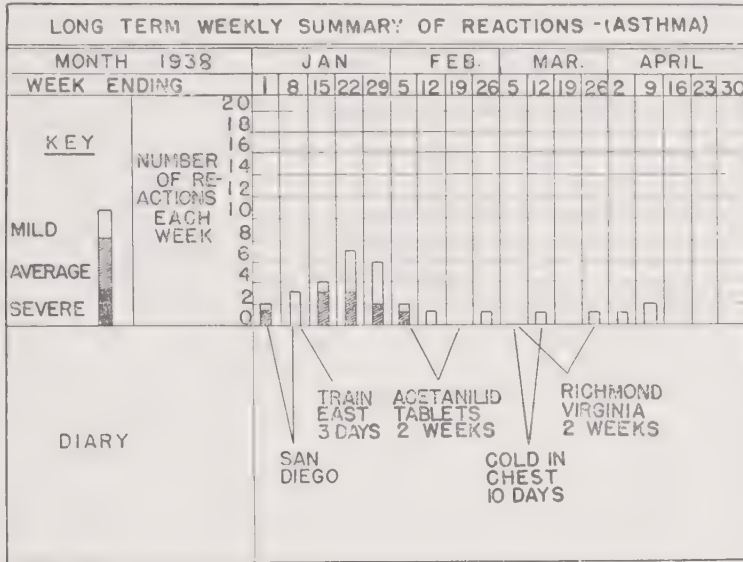


Fig. 67.—Long term chart continued. This carries the same patient (see Fig. 71) into the third year. Here, progress becomes very manifest, the usual period of increased severity (February to May) having become one of near-freedom from symptoms. A later report (Feb. 1939) describes continuation of complete relief.

the patient did not happen to eat some particular foods that would have caused trouble. However, watch will be maintained for subsequent symptoms due to such foods. Assuming, therefore, that the patient has been relieved, the next task will be to add those foods which have been unnecessarily prohibited. This applies especially to "false positive" foods. Food additions are now carried out, each food being added separately, with a build-up, as described. The Diary is continued while foods are being added. In the event of recurrence the food factor usually shows up very clearly in the Diary.

It should be borne in mind that if dietary restrictions are numerous and long continued, appropriate steps should be taken to ensure an adequately balanced diet with sufficient quantity of the food elements, minerals and vitamins to guard against nutritional deficiency.

CHAPTER XXXII

THE ELIMINATION DIET

We are indebted to Rowe for the elaboration of the elimination diet often used in food allergy. Rowe points out that the idea is not new and quotes a long list of men who have suggested rigidly restricted diets in the treatment of allergic symptoms. The list begins with Salmon who in 1913 described what might be termed an elimination diet for the treatment of urticaria. This diet contained tea, coffee, sugar, bouillon, lemon or grape juice, brown bread, butter, rice, barley, oatmeal, green vegetables, potatoes and fresh or cooked fruit. Other recommended diets have been either positive or negative in their specifications. Positive diets, those which designate foods to be eaten, included such as bread, milk and beef (Coke); rice and water, to which other foods are later added (Andresen); rice and tea, with later additions (Van Leeuwen). Negative diets have for the most part consisted of the recommendation that frequently allergenic foods such as wheat, egg and milk be avoided.

Rowe, however, added greatly to the feasibility of the elimination diet by providing a series of alternative positive lists easily prescribed and easily followed by the patient.

Proper use.—He states, "When symptoms of probable food allergy are not controlled by diets which exclude foods to which skin reactions have occurred, or if skin reactions to foods are negative, or impossible to perform, elimination diets may be used." The elimination diet may be tried tentatively even prior to the performance of skin tests. If one or another of Rowe's diets relieves symptoms, much painstaking and time-consuming study will be avoided. If symptoms are not relieved by any of the elimination diets, his suggestions concerning supplemental elimination diets may be tried. Even then, without relief, one must not conclude that food allergy is not playing a part. One must then have recourse to the more detailed methods described in preceding chapters. There is no reason why elimination diets should not be tried first if the physician prefers to do so, although it appears to the writer more logical to obtain as much information concerning the patient's reactions, from objective methods of study, prior to the institution of any form of trial diet. This obviates the difficulty, possibly embarrassment, of having prescribed a certain food in a trial diet which some time later, on testing, is found to be strongly positive. Rowe does not insist that the elimination diet supplant the skin test but makes the very proper suggestion that if the circumstances are such that skin tests cannot be performed at the time, the physician may proceed with the elimination diet, more or less as a preliminary effort which in some cases may be found to be all that is necessary.

As the name implies, the procedure is based on the selection of a list of those foods which have been shown by experience to be relatively infrequently allergenic. The frequently allergenic foods are eliminated. For simplification only one or at most few representatives of the various culinary groups are included in each list.

The first diet selected will therefore be a trial diet containing foods to which most persons are not allergic. It may or may not contain foods to which the particular patient is allergic. If it does not, and if the symptoms

are due entirely to food allergy, they will be relieved. If after trial of from two to four weeks, relief has not been achieved, another of the elimination diets may be tried, one which again contains infrequently allergenic foods, but altogether different foods from those used in the first list. In this way, with successive trials, a diet may be found suitable for the patient. When this has been accomplished, food additions may be made as described in the escalator diet (Chapter XXXIII).

Rowe's first series.—When the Rowe elimination diet is used after skin testing, positively reacting foods may be removed from the list, and others which have given negative skin reactions may be substituted. The individualized elimination diet then becomes a foundation list upon which food additions may be built for the purpose of ultimately attaining an adequately balanced nonallergenic diet. Rowe's first series comprised five diets which were later reduced to four. Each contained representatives of the various culinary groups, the more important of which appeared each time in only one diet. The fifth diet was milk alone. The original schedule was, from the writer's point of view, open to two criticisms. It listed foods which Rowe had found infrequently allergenic in California. The importance of various foods varies in different sections of the world, depending upon the customary diet of the community. Some foods which Rowe had found infrequently allergenic were found by Vaughan to be of distinct allergenic importance in Virginia.

The second criticism was that biologically related foods appeared in all of the first four diets. This is seen especially with peach, apricot and prune, less noticeably so with carrot and celery and with spinach and beet.

New series.—I feel that Rowe's latest diet series (1944) adequately avoids both of these drawbacks.

There are four diets from which to select. Diet 4 contains milk alone. Diet 3 contains a variety of foods but no milk, egg, wheat or any of the other cereals. Thus Rowe has avoided the possibility of crossed reactions among the members of the cereal family. Diets 1 and 2 are both fairly generous. Foods belonging to the same biologic group appear in the same diet rather than being crossed in the diets. Thus lemon and grapefruit are in the first, and in the second peach, pear and prune comprise the genetically related fruits. Spinach and beet appear in Diet 1, while peas and beans are in Diet 2.

There appears to be no food to which a person may not ultimately become sensitized. We therefore cannot speak of a completely nonallergenic diet. Rowe's Diet I certainly contains foods which we find in Virginia to be less frequently allergenic. Rice in our experience is the least frequently allergenic of the cereals. It will be seen from Table XXVI showing the allergenic frequency of foods in series studied by Rowe and by Vaughan, that all foods in Diet 1 show an allergenic incidence of less than approximately 5 per cent. There is therefore a fair chance that such a diet will eliminate all of the positive foods in a given case. With the exception of tomato and plum-prune, this holds also for Diet 2. Employment of one or the other diets, successively if necessary, offers a reasonable chance of finding a dietary program which will relieve the patient. Both failing, one may change to Diet 4, milk only, which contains none of the ingredients of Diets 1 or 2. If No. 4 gives relief, additions may be made successively out of Diets 1 and 2. Diet 3 contains representatives of Nos. 1 and 2, but is entirely devoid of the cereal grains, egg and milk.

TABLE XXVI.—ALLERGENIC FREQUENCY OF SOME ELIMINATION DIET FOODS

FOOD	VAUGHAN'S SERIES	ROWE'S SERIES
	Per Cent	Per Cent
Apricot	5.5	4
Artichoke	-	1
Asparagus	5.5	0.5
Beef, veal	2	2
Beet	-	-
Carrot	3	5
Chicken	3.4	1
Corn	4	2
Cottonseed	6	1
Grapefruit	3	4
Lamb	3	2
Lemon	2.5	2
Lettuce	3.5	4
Lima bean	6	1
Olive	-	2
Pea	3	1
Peach	5	4
Pear	3	-
Pineapple	1.5	2
Plum, prune	7	1
Pork	1.5	5
Potato	9.5	6
Rice	2.5	4
Rye	3.5	3
Spinach	5.5	-
Squash	3.5	4
String bean	3.5	1
Sweet potato	1.5	2
Tomato	7	9

According to Rowe, relief is obtained at times with Diet 3. Since there is definite evidence of crossed relationship at times between the cereal grains, Rowe's Diet 3 appears to me to be a much more logical elimination program than that frequently used in which the doctor tells the patient to avoid wheat, egg, and milk. The avoidance of wheat, egg, and milk, plus the cereal grains should be more effective among those who are so unfortunate as to be allergic to these three staples.

As has been pointed out by Withers in the preceding discussion of the biologic grouping, there is evidence of crossed reactivity among the cereal grains, but it is rare to find a person allergic to all of them. If therefore a patient is relieved on Diet 3, the cereal grains will be added one after another with the probability that he will tolerate at least some of them.

Diet 4 follows the principle of the escalator program, described in the next chapter. It represents the application in allergy of a procedure previously followed in other diseases. Arthur Hurst (1919) in discussing the treatment of mucous colitis which at that time was not considered as possibly allergic, wrote, "In exceptionally severe cases it is advisable to begin the treatment with an absolutely unstimulating and completely digestible diet, such as milk, to which arrowroot or other cellulose-free carbohydrates can be added."

The idea of starting with a single food, when one does not know what food is responsible for symptoms is logical. The best food to select would be that which contains the food elements in approximately proper proportion for the maintenance of nutrition. Among the single foods milk fulfills this

specification better than others. Unfortunately many are allergic to milk. In this case other elimination diets may be tried. Or, one may start with any other single food.

In Diet 4 as in the other three it should be emphasized that the diet is not a permanent maintenance menu. They are not adequately balanced, and food additions should be made as rapidly as is reasonably possible consistent with results.

One should also bear in mind that a person who is not allergic to milk may have trouble from milk. Allergenic foodstuffs eaten by cattle have been found to cause symptoms in persons ingesting that particular milk.

When milk is permanently deleted from the diet, calcium should be prescribed. This element is not found in sufficient abundance in a variety of other foods. It need not be given in organic form. Campbell has recently shown that inorganic calcium is adequately utilized.

TABLE XXVII—ELIMINATION DIETS (ROWE)*

<i>Diet 1</i>	<i>Diet 2</i>	<i>Diet 3</i>	<i>Diet 4</i>
Rice	Corn	Tapioca	Milk†
Tapioca	Rye	White potato	Tapioca
Rice biscuit	Corn pone	Breads made of soy,	Cane sugar
Rice bread	Corn-rye muffin	lima and potato	
	Rye bread	starch and tapioca	
	Ry-Krisp	flours	
Lettuce	Beets	Tomato	
Chard	Squash	Carrot	
Spinach	Asparagus	Lima bean	
Carrot	Artichoke	String bean	
Sweet potato		Peas	
Lamb	Chicken (no hens)	Beef	
	Bacon	Bacon	
Lemon	Pineapple	Lemon	
Grapefruit	Peach	Grapefruit	
Pears	Apricot	Peach	
	Prune	Apricot	
Cane sugar	Cane or beet sugar	Cane sugar	
Sesame oil	Mazola oil	Sesame oil	
Olive oil	Sesame oil	Soy bean oil	
Salt	Salt	Salt	
Gelatin, plain,	Gelatin, plain	Gelatin, plain or lime	
lime or lemon	or pineapple	or lemon	
Maple syrup or syrup	Karo corn syrup	Maple syrup or syrup	
made with cane sugar	White vinegar	made with cane	
flavored with maple	Royal baking powder	sugar flavored with	
Royal baking powder	Baking soda	maple	
Baking soda	Cream of tartar	Royal baking powder	
Cream of tartar	Vanilla extract	Baking soda	
Vanilla extract		Cream of tartar	
Lemon extract		Vanilla extract	
		Lemon extract	

†Milk should be taken up to two or three quarts a day. Plain cottage cheese and cream may be used. Tapioca cooked with milk and milk sugar may be taken.

Use of "Elimination Diets"*

"When symptoms of probable food allergy are not controlled by diets which exclude foods to which skin reactions have occurred, or if skin reactions to foods are negative, or impossible to perform, 'elimination diets' may be used. The frequency of the negative

*From Rowe, Albert H.: *Elimination Diets and Patient's Allergies*, Lea & Febiger, Philadelphia, 1944.

skin reaction to foods productive of clinical allergy and the occurrence of positive reactions to foods not causative of allergic symptoms must be remembered.

"1. Diets 1 and 2 first may be prescribed together or separately, modifying them by substituting similar foods for any in the diets to which skin reactions or known idiosyncrasies exist. Allergic incompatibility to the foods in such trial diets may be studied with the leukopenic index if desired while diet trial continues.

"2. If sensitization to cereals as a group is suspected, use the cereal-free elimination diet.

"3. Suggested menus for Diets 1 and 2 together and for Diets 1, 2, and 3 separately are detailed later. These menus indicate the ease of preparing meals which meet caloric and metabolic requirements with foods in the 'elimination diets.' A reduction of calories and a modified preparation of specified foods are indicated for children according to age.

"4. The selected diet must be taken for at least ten days or even three or four weeks, for in many cases reacting bodies to the causative foods disappear very slowly from the shock tissues. If relief does not occur another 'elimination diet' should be tried.

"5. Absolute adherence to the prescribed diet is imperative. Not the slightest bit of any food not specified must be taken. Restaurant and hotel food often contains slight amounts of forbidden foods, due at times to poorly cleansed cooking utensils or carelessness in cooking. No commercial breads, cookies, soups, etc., should be used unless every ingredient is known. Margarine contains 2 to 6 per cent milk solids.

"6. If body weight decreases, specified sugars, starches and oils must be increased. Prescribed fruits and vegetables assure Vitamins A, B, C and G. Adequate protein, when milk is excluded, requires meat or other protein two or three times a day. If milk is excluded longer than one month, the addition of 4 to 6 grams of dicalcium phosphate on retiring will assure mineral balance. Vitamin D must be supplemented by the use of cod liver oil, halibut oil, viosterol, sun or quartz light therapy. Until fish is added, fish oils cannot be used, and viosterol should be allowed only in an oil contained in the 'elimination diets.'

"7. With relief of symptoms for longer than former periods of freedom, other foods, one to three at a time, from the remaining 'elimination diets' are tried every four to seven days. Thereafter, other vegetables, fruits, meats, spices and nuts gradually may be added. In one to three months, milk, egg and wheat may be tried, separately, at fortnightly intervals. If the patient is allergic to any food, symptoms may occur immediately, or in days or even weeks according to the patient's tolerance. In such cases the food must again be eliminated.

"8. In the undernourished or in children, Diet 4 containing milk may be used first or milk may be tried, added to the chosen 'elimination diet' after one or two weeks. Sobee, a soya bean product, Cemac, containing beef and vegetables or almond milk, are available for infants and children who cannot tolerate denatured cow's or goat's milk.

"9. Desensitization by elimination of a food may require weeks, months, or even years. With the above precautions, however, caloric and metabolic requirements are assured.

"10. The diagnosis, control and treatment of inhalant and contact allergies which may accompany food sensitizations are most important and not infrequently are necessary for satisfactory control of a food allergy.

"Supplemental Elimination Diets.—When Diets 1, 2 and 3 fail to relieve symptoms, then supplemental diets may be tried. Or they may be used initially if sensitizations to many different foods or to nearly all members of one or more groups of foods such as cereals, fruits, vegetables, or meats are indicated by history or skin reactions.

"In the unsolved case of possible food allergy all foods must be suspected and minimal diets be selected as follows:

"1. A choice of one or two of the following carbohydrates: Rice, corn, tapioca, sago, sweet or white potato.

"2. A choice of one or two of the following protein rich foods: Lamb, beef, chicken, soya bean, nutramigen.

"3. A choice of two or three of the following vegetables: Spinach, carrot, beet, artichoke, asparagus, pea, tomato, string bean.

"4. A choice of one or two of the following fruits: Lemon, grapefruit, pear, peach, apricot, pineapple.

"5. Mazola (corn), olive or sesame oil, white sugar, maple syrup or corn glucose, salt.

"6. Tea, mate (Brazilian tea) or the juice of tomato or any fruit included in the diet.

“The choice of the supplemental diet depends on the patient’s history of food idiosyncrasies or any positive skin reactions, if testing is available, and on the clinical reactions to foods evident from diet trial.”

CEREAL-FREE ELIMINATION DIET (ROWE)

Tapioca	Carrot	Cane or beet sugar
White potato	Beet	Salt
Sweet potato	Artichoke	Sesame oil
Lima bean-potato bread	Tomato	Soy bean oil
Soy bean-lima bean bread	Squash	Sesame spread
Soy bean-potato-tapioca bread	Asparagus	Gelatin, plain
Lamb	Peas	Lime, lemon or pineapple gelatin
Beef	String bean	Maple syrup or syrup made with cane sugar flavored with maple
Chicken (no hens)	Lima bean	White vinegar
Bacon	Lemon	Vanilla extract
Liver (calf, beef or lamb)	Grapefruit	Lemon extract
Lettuce	Pear	Royal baking powder
Spinach	Pineapple	Baking soda
Chard	Peach	Cream of tartar
	Apricot	
	Prune	

SUGGESTED MENUS FOR THE “ELIMINATION DIETS” (ROWE)

BREAKFAST

Diets 1 and 2

		Approximate amounts
<i>Beverage</i>	(a) Grapefruit (fresh) juice or lemonade with sugar as desired.	1 glassful
	(b) Pineapple juice.	
<i>Cereal</i>	(a) Boiled brown or polished rice or cooked corn meal served with apricot, peach or prune juice and sugar.	$\frac{1}{2}$ cup rice 3 teaspoonfuls juice or
	(b) Rice Krispies or corn flakes served with grapefruit juice and sugar or with apricot, peach or prune juice or maple syrup.	$\frac{3}{4}$ cup dry flakes
	(c) Cold rice or corn meal fried in Mazola oil or bacon or chicken fat served with maple syrup or Karo corn syrup.	
<i>Meat</i>	(a) Bacon (mod. crisp) or	3 slices or
	(b) Lamb chops, lamb or chicken croquettes (1)	1 med. chop
	(c) Lamb kidney or liver fried with bacon	
<i>Bread</i>	(a) Corn pone (2)	2 muffins or 2 slices toasted
	(b) Corn rice muffin (3)	
	(c) Corn rye muffin (4)	
	(d) Rice biscuit (5)	
	(e) Rice bread (6)	
	(f) Rye bread (7)	
	(g) Ry-Krisp	
<i>Jams or Preserves</i>	(a) Peach or prune jam	2 tablespoonfuls
	(b) Apricot or apricot pineapple jam or preserves	
	(c) Grapefruit and lemon marmalade	
	(d) Pear butter (9)	
<i>Fruit</i>	Sliced or whole grapefruit, canned, fresh or stewed peaches, apricots, pears, pineapple or prunes.	

NOTES.—Choices as indicated by letters are offered in all menus though more than one may be used if desired. *Chicken meat and fat* should come only from broilers or roosters. Hens frequently have egg on them as a result of breaking unlaid eggs in dressing them. *Breads, muffins and cookies* should be made at home or by bakers who follow the recipes or similar ones as given in these diets. *Rye flour* especially is apt to be mixed with wheat and commercial rye bread practically always contains wheat and milk. *Corn meal* can be obtained in different degrees of fineness.

This menu contains approximately calories 612.

Gm. of carb.	92	Gm. of Ca	0.104
Gm. of protein	16	Gm. of P	0.200
Gm. of fat	20	Gm. of Fe	0.0027

LUNCH OR DINNER

Diets 1 and 2

		Approximate amounts
<i>Salad</i>	(a) Lettuce with apricot, peach, pear or pineapple with oil dressing and lemon juice or special mayonnaise (23)	2 halves or slices or
	(b) Vegetable salad made of tomato, carrots, beets, asparagus, peas, string beans or artichokes with oil dressing or special mayonnaise.	$\frac{1}{2}$ cup mixed vegetables 1 T oil or dressing
	(c) Lettuce with oil dressing.	
	(d) Lemon gelatin with grated carrots and crushed pineapple.	
<i>Soup</i>	(a) Lamb broth clear or with rice, carrot, peas, string beans as desired.	1 cup
	(b) Chicken broth clear or with rice, carrot, peas, string beans as desired.	
<i>Meat</i>	(a) Lamb served as chops, roast, tongue or stew with lamb, rice, corn, carrots, peas, beets or string beans.	2 med. chops or
	(b) Chicken—roasted, fried, broiled, stewed. May be rubbed with bacon if desired or stuffed with rice or corn meal.	1 broiler or equivalent
	NOTE.—Thicken gravy or sauces with rice flour or corn-starch.	
<i>Vegetables</i>	Spinach, carrots, squash, asparagus, artichokes, beets.	4 T vegetables
<i>Bread</i>	Choice of those in breakfast.	
<i>Jams or Preserves</i>	Choice of those in breakfast.	
<i>Dessert</i>	(a) Fruit as suggested for breakfast.	4 T fruit
	(b) Rice fruit pudding (10).	1 cup cake
	(c) Tapioca fruit pudding (11).	
	(d) Corn-rice cookie or rice cup cakes (12).	
<i>Beverage</i>	(a) Grapefruit juice or lemonade with sugar. Corn dextrose may be used if extra carbohydrates are desired.	1 glassful

NOTES.—It is best to use canned, preserved or *fresh cooked* fruits. Uncooked fruits, other than grapefruit or lemon, are more apt to produce allergic reactions than heated fruits. Dried fruits well cooked with the exception of prunes are not well tolerated by certain patients. *Soups* may be made only with ingredients in the prescribed diets. Canned soups and those in restaurants and hotels are apt to have wheat, egg or other forbidden ingredients. *Meats* must not be cooked or basted with any food such as wheat flour, butter or spices not allowed. *Gravies* must be thickened only with prescribed flours. *Gelatin* may be incorporated in salads and desserts if desired.

Salted Crisco or yellow vaseline is accepted by some as butter substitutes.

This menu contains approximately—calories 864. Total per day—2340 cal.

Gm. of carb.	125	Gm. of Ca	0.211
Gm. of protein	28	Gm. of P	0.547
Gm. of fat	28	Gm. of Fe	0.0091

BREAKFAST

Diet 1

		Approximate amounts
<i>Beverage</i>	(a) Grapefruit juice or lemonade with sugar as desired	1 glassful
	(b) Pear juice flavored with lemon.	1 glassful
<i>Cereal</i>	(a) Boiled or steamed brown or polished rice served with pear juice or maple syrup and sugar.	$\frac{1}{2}$ cup cooked rice 3 T syrup
	(b) Rice flakes or Rice Krispies served with pears or pear juice and sugar.	$\frac{3}{4}$ cup Rice Krispies 4 T juice
	(c) Tapioca cooked in water and flavored with lemon juice, lemon rind and sugar.	1 T dry tapioca for one serving
	Lamb chops or liver patties (13).	2 med. chops
<i>Bread</i>	(a) Rice biscuits (5).	2 biscuits
	(b) Rice bread (6).	
<i>Jam or Preserves</i>	(a) Pear butter (9).	2 tablespoonfuls
	(b) Lemon or grapefruit marmalade.	
<i>Fruit</i>	(a) Sectioned or whole grapefruit.	1 grapefruit
	(b) Fresh or canned pears.	3 halves

NOTE.—Corn sensitive patients might react to corn oil or glucose which must be excluded even in minute amounts.

This menu contains approximately—calories 768.

Gm. of carb.	118	Gm. of Ca	0.089
Gm. of protein	29	Gm. of P	0.400
Gm. of fat	20	Gm. of Fe	0.0046

LUNCH OR DINNER

Diet 1

		Approximate amounts
<i>Salad</i>	(a) Hearts of lettuce. Dressing of olive oil, and lemon.	$\frac{1}{2}$ med. head 1 T oil
	(b) Vegetable salad of lettuce, carrots, and olives as desired with above dressing or special mayonnaise (23).	1 cupful mixed veg. $\frac{1}{2}$ grapefruit or 2 halves of pears
	(c) Lettuce with sectioned grapefruit or pears served with oil and lemon juice dressing.	
<i>Soup</i>	Lamb broth clear or with tapioca or rice and carrots as desired.	1 cupful
<i>Meat</i>	(a) Lamb served as chops, roast, tongue.	2 med. lean chops or their equivalent
	(b) Stew made with lamb, rice or tapioca, or carrots. Thicken gravy with rice flour.	
<i>Vegetables</i>	Steamed or boiled rice, brown or polished.	$\frac{1}{2}$ cup cooked
<i>Bread</i>	Spinach, carrots, artichokes, chard, sweet potato.	4 T
<i>Jam or Preserves</i>	Choice of those suggested for breakfast.	
<i>Dessert</i>	(a) Plain lemon or lime gelatin with pears or grapefruit as desired.	
	(b) Winter pears baked with maple syrup or brown sugar.	1 large pear
	(c) Rice cookie or cup cakes (12), (18).	1 cup cake
	(d) Puffed rice candy (14).	
	(e) Tapioca fruit pudding (11).	
	(f) Rice fruit pudding (10)	
<i>Beverage</i>	Choice of those suggested for breakfast.	1 glassful

NOTE.—Pure olive oil and Wesson oil only can be used in Diet 1. Imported oil may be adulterated. Wesson oil and Crisco must be excluded in presence of positive reactions or of clinical allergy to cottonseed.

This menu contains approximately—calories 914 Total calories for day—2596

Gm. of carb.	129	Gm. of Ca	0.249
Gm. of protein	32	Gm. of P	0.557
Gm. of fat	30	Gm. of Fe	0.0100

BREAKFAST

Diet 2

		Approximate amounts
<i>Beverage</i>	(a) Pineapple or prune juice.	1 glassful
	(b) Apricot, peach and pineapple juices mixed.	1 glassful
<i>Cereal</i>	(a) Corn flakes served with pineapple juice, or with peach, apricot or prune juice and sugar.	4 T juice $\frac{3}{4}$ cup corn flakes
	(b) Corn meal mush served with maple or Karo syrup.	$\frac{1}{2}$ cup cooked cereal
	(c) Cold corn meal mush fried in Mazola oil or bacon fat served with syrup and bacon.	
<i>Meat</i>	(a) Bacon.	4 med. strips bacon
<i>Bread</i>	(b) Chicken croquettes (1).	1 croquette
	(a) Corn pone (2).	2 muffins
	(b) Corn and rye muffin (3).	
	(c) Rye bread (7).	2 thin slices toasted
<i>Jam or Preserves</i>	(d) Ry-Krisp (8).	2 Ry-Krisp
	(a) Pineapple preserves.	2 tablespoonfuls
<i>Fruit</i>	(b) Apricot or peach jam.	
	Fresh, cooked or canned pineapple, peaches, apricots or prunes.	to $\frac{3}{4}$ cup

This menu contains approximately—calories 856.

Gm. of carb.	149	Gm. of Ca	0.092
Gm. of protein	20	Gm. of P	0.279
Gm. of fat	20	Gm. of Fe	0.0042

LUNCH OR DINNER

Diet 2

		Approximate amounts
<i>Salad</i>	(a) Asparagus with Mazola or sesame oil and white vinegar or special mayonnaise (23).	1 large tomato and 6 to 8 stalks of asparagus
	(b) Vegetable salad with asparagus, beets, and artichokes as desired with above oil dressing.	2 T oil 1 cupful mixed veg.
	(c) Combination fruit salad of pineapple, peaches and apricots with special mayonnaise thinned with pineapple juice.	1 cupful mixed fruits
	(d) Chicken and pineapple salad mixed with special mayonnaise (16).	
<i>Soup</i> <i>Meat</i>	(a) Chicken broth clear.	1 cupful
	(a) Chicken—roasted, fried, broiled, stewed. May be brushed with Mazola oil and rolled in corn meal if desired. Serve broiled peaches, apricots or pineapple with fried or broiled chicken.	½ broiler or fryer or its equivalent
	(b) Chicken livers rolled in cornstarch or corn meal and sautéed in Mazola or Wesson oil.	
<i>Vegetables</i>	Squash, asparagus, corn, beets.	4 tablespoonfuls
<i>Bread</i>	Choice of those suggested for breakfast.	
<i>Jam or</i> <i>Preserves</i>	Choice of those suggested for breakfast.	
<i>Dessert</i>	(a) Fruits as suggested for breakfast.	4 tablespoonfuls
	(b) Rye cookies (18).	2 or 3 cookies
	(c) Fruit cornstarch pudding with crushed pineapple (19).	3 tablespoonfuls
	(d) Jellyed prunes with pineapple.	

This menu contains approximately—calories 1006

Total calories for day—2868

Gm. of carb.	118	Gm. of Ca	0.138
Gm. of protein	30	Gm. of P	0.522
Gm. of fat	46	Gm. of Fe	0.0092

BREAKFAST

Diet 3

		Approximate amounts
<i>Beverage</i>	(a) Grapefruit juice or lemonade with sugar as desired.	1 glassful
	(b) Tomato juice.	1 glassful
<i>Cereal</i> <i>Substitute</i>	(a) Tapioca cooked with apricot or peach, or flavored with lemon, maple sugar or caramelized sugar (20).	1 T dry tapioca ½ cupful
	(b) Lima bean flakes served with apricot, peach, grapefruit juice and sugar as desired.	¾ cupful flakes 4 T juice
<i>Meat</i>	(a) Bacon—moderately crisp.	4 slices
	(b) Beefsteak, chipped beef, beef patties or tongue.	Small steak or its equivalent
<i>Bread</i>	(c) Bacon and hashed brown potatoes.	
	(a) Lima bean-potato bread (21).	2 slices toasted
<i>Jams or</i> <i>Preserves</i>	(b) Lima bean-soya bean muffins (22).	2 muffins
	(a) Lemon or grapefruit-carrot marmalade (26).	2 tablespoonfuls
<i>Fruit</i>	(b) Peach or apricot jam.	
	(c) Tomato preserves flavored with lemon.	
	(a) Sliced or whole grapefruit.	1 grapefruit
	(b) Fresh, stewed or canned peaches or apricots.	4 tablespoonfuls
	(c) Sliced tomatoes with sugar.	

This menu contains approximately—calories 922.

Gm. of carb.	149	Gm. of Ca	0.130
Gm. of protein	23	Gm. of P	0.500
Gm. of fat	26	Gm. of Fe	0.0078

LUNCH OR DINNER

Diet 3

		Approximate amounts
Salad	(a) Sliced tomato with olive or Wesson oil and lemon juice dressing or sugar.	1 large tomato 1 T oil
	(b) Vegetable salad of carrots, lima beans, string beans, olives or tomatoes as desired with special mayonnaise (23).	1 cupful mixed vegetables
	(c) Fruit salad made of grapefruit, peaches or apricot with above dressings.	$\frac{1}{2}$ to $\frac{3}{4}$ cupful of fruit.
Soup	(a) Beef bouillon clear or with carrots, lima beans or tomato.	1 cupful
	(b) Lima bean soup flavored with bacon (24).	
Meat	(a) Beefsteak, roast or tongue.	Average liberal serving of meat
	(b) Beef stew with potato, carrots, lima beans or string beans. Thicken gravy with potato flour.	
	(c) Calf or beef liver and bacon.	
Vegetables	(a) White potatoes.	1 med.-sized potato
	(b) Carrots, lima beans, string beans, tomatoes, peas.	$\frac{1}{2}$ T
Bread	Choice of those suggested for breakfast.	
Jams or Preserves	Choice of those suggested for breakfast.	
Dessert	(a) Fruits as suggested for breakfast.	4 T
	(b) Tapioca fruit pudding (20) or (11).	
	(c) Lima bean-potato flour cookies or cup cakes frosted with sugar and lemon juice icing (25).	2 cookies or 1 cup cake
Beverage	(a) Grapefruit juice or lemonade with sugar as desired.	1 glassful
	(b) Tomato juice.	

This menu contains approximately calories 901

Total calories for day—2724

Gm. of carb.	140
Gm. of protein	38
Gm. of fat	21

Gm. of Ca	0.326
Gm. of P	0.059
Gm. of Fe	0.0190

RECIPES

(1) *Chicken Croquettes*

1 tablespoonful oil or chicken fat
2 tablespoonfuls cornstarch
 $\frac{1}{2}$ cup liquid (chicken broth)
 $\frac{3}{4}$ cup cooked minced chicken
Salt

Make a sauce of fat, cornstarch and liquid. Add the other ingredients. (Cooked cornmeal may be added.) Cool, shape, dip in rye flour or crushed corn flakes. Bake in medium oven or fry in deep fat.

(2) *Corn Pone**

1 cup cornmeal
 $\frac{1}{2}$ teaspoonful salt
Boiling water
1 tablespoonful Mazola oil

Carefully pour enough boiling water onto the cornmeal to make a stiff mixture, stirring constantly. Add the oil and mix well. Mold into oblong "pones" and fry in hot skillet with enough fat to prevent sticking. When brown on one side, turn and brown on the other side. Serve hot.

(3) *Corn and Rice Muffins**

$\frac{1}{2}$ cup rice flour
 $\frac{1}{2}$ cup yellow cornmeal
2 tablespoonfuls sugar
 $2\frac{1}{2}$ teaspoonfuls baking powder
 $\frac{3}{4}$ tablespoonfuls Mazola oil
 $\frac{1}{2}$ cup water

Mix all the dry ingredients well, sifting them together four or five times. Add the water and oil. Bake in a hot oven twenty minutes. Makes six small muffins.

(4) *Corn and Rye Muffins**

Use the above recipe but substitute rye flour for rice flour.

*Fat used in recipes for greasing pans or shortening must only be oil or fat specified in the prescribed diet. Baking powder should be Royal or Schilling which contain no egg.

(5)

Rice Biscuits

Made by the Battle Creek Sanitarium.

(6)

*Rice Bread**

1 cup rice flour
 3 teaspoonfuls baking powder
 2 tablespoonfuls bacon fat or oil
 1 tablespoonful sugar
 $\frac{1}{2}$ teaspoonful salt
 $\frac{3}{4}$ cup water

Sift the dry ingredients. Add water and fat.
 Bake in a loaf pan in a moderate oven.

(7)

*Rye-Rice Bread**

$\frac{1}{2}$ cup rye flour
 $\frac{3}{4}$ cup rice flour
 $\frac{1}{2}$ teaspoonful salt
 6 teaspoonfuls sugar
 5 teaspoonfuls baking powder
 2 teaspoonfuls olive oil
 $1\frac{1}{2}$ cups water

Sift all the dry ingredients together. Add water and oil. Bake in a loaf pan in a moderate oven for forty minutes.

(8)

Ry-Krisp

Prepared by the Ralston Purina Company.

(9)

Pear Butter

Select firm, ripe pears. Peel, core and cut into rather small pieces. To two cups of prepared fruit add one cup of sugar. Cook slowly, stirring frequently to prevent burning, for two hours or until the mixture is quite thick.

(10)

Rice-Fruit Pudding

Sauce:
 1 cup sugar
 2 tablespoonfuls rice flour
 $\frac{1}{2}$ teaspoonful salt
 $1\frac{1}{4}$ cups boiling water
 1 teaspoonful lemon juice or vanilla

Mix sugar, salt and cornstarch. Add water and cook until thick. Remove from stove and add flavoring. Add boiled rice and apricots or sliced peaches and serve warm. Reserve some sauce to pour over the pudding.

(11)

Tapioca-Fruit Pudding

2 halves peaches sliced
 1 tablespoonful dry tapioca
 2 teaspoonfuls sugar
 $\frac{1}{2}$ cup peach juice and water

Drain peaches and sprinkle with one teaspoonful sugar. Cook tapioca in juice and water until it is clear. Add remaining sugar and salt. Line a baking dish with peaches. Fill with tapioca and bake in a moderate oven twenty minutes.

(12)

*Rice Cup Cakes**

$\frac{3}{4}$ cup hot water
 $1\frac{1}{2}$ cups rice flour
 2 level tablespoonfuls shortening
 $\frac{1}{2}$ cup sugar
 $\frac{1}{4}$ teaspoonful salt
 3 level tablespoonfuls baking powder
 1 teaspoonful vanilla

Pour hot water over half the flour. Cream sugar and shortening and add to the above mixture, beating well. Add the other ingredients, mixing well. Bake in muffin pans about twenty minutes in a fairly hot oven.

(13)

Lamb Patties

Ground lamb pressed into small patties. Broiled or fried.

*Fat used in recipes for greasing pans or shortening must only be oil or fat specified in the prescribed diet. Baking powder should be Royal or Schilling which contain no egg.

(14)

Puffed Rice Candy

1 cup sugar
 $\frac{3}{4}$ cup brown sugar
 1 cup water
 $\frac{1}{4}$ teaspoonful salt
 1 teaspoonful vanilla
 Puffed rice

Cook sugar, syrup and water until brittle. Add vanilla and salt. Pour puffed rice, stirring all the time so that the kernels will be evenly coated. Turn it into a greased pan and cut in squares. Keeps well in an air-tight container.

(15)

Tomatoes Cooked With Sugar

Select firm, ripe tomatoes. Remove the skins, cut in slices and drain an hour or more. For each cup of tomatoes add a cup of sugar and boil until thick, stirring often. Sliced lemon may be added to the tomatoes while cooking.

(16)

Chicken and Pineapple Salad

Cut cold boiled chicken into cubes and marinate for two hours in French dressing of oil and white vinegar and salt. Drain well, mix chicken with about $\frac{1}{3}$ its volume of diced pineapple and add special mayonnaise, thinned with pineapple juice to taste.

(17)

Split Pea Soup

1 cup split peas
 1 tablespoonful bacon fat
 Diced bacon (crisp)
 Salt

Cook the peas until they form a smooth purée. Just before serving, add salt, bacon fat and crispy fried bacon.

(18)

Rye or Rice Cookies

1 cup rye or rice flour
 $\frac{1}{2}$ cup light molasses (or syrup)
 3 tablespoonfuls Wesson oil
 $\frac{1}{4}$ teaspoon salt
 $\frac{1}{2}$ teaspoonful soda
 $1\frac{1}{2}$ teaspoonfuls baking powder
 1 tablespoonful sugar
 Water to make a stiff dough

Mix dry ingredients. Add syrup, oil and water. Drop on a greased cookie sheet and bake at 325° for fifteen minutes.

(19)

Fruit Cornstarch Pudding

$1\frac{1}{2}$ cups fruit pulp
 $1\frac{1}{2}$ cups water
 2 teaspoonfuls sugar
 5 level teaspoonfuls cornstarch

Cook for $\frac{1}{2}$ hour in the top part of a double boiler.

(20)

Tapioca With Apricots

6 halves apricots, puréed
 2 teaspoonfuls sugar
 1 tablespoonful dry tapioca
 $\frac{1}{2}$ cup juice and water

Cook the liquid and tapioca in a double boiler until tapioca is clear. Add apricots and blend well. Serve warm with apricot juice.

(21)

*Lima Bean-Potato Muffins or Bread**

$\frac{3}{4}$ cup potato flour
 $\frac{1}{2}$ cup lima bean flour
 3 teaspoonfuls baking powder
 $\frac{1}{2}$ teaspoonful salt
 4 teaspoonfuls sugar
 $\frac{1}{2}$ cup water
 2 tablespoonfuls shortening

Sift dry ingredients together. Melt fat and add to water, add slowly to dry ingredients. Put in greased muffin tins and bake at 400° F. for 20 minutes. Serve hot. Makes 10 small muffins.

(22)

Lima Bean-Soya Bean Bread

Substitute soya bean flour for potato flour in recipe for potato-lima bean bread.

*Fat used in recipes for greasing pans or shortening must only be oil or fat specified in the prescribed diet. Baking powder should be Royal or Schilling which contain no egg.

(23)

Boiled Mayonnaise

1 teaspoonful sugar
 $\frac{1}{2}$ teaspoonful salt
 3 level teaspoonfuls starch†
 Juice 1 large lemon
 $\frac{7}{8}$ cup boiling water
 $\frac{1}{2}$ cup Mazola oil

Mix sugar, salt, starch and lemon juice. Add water, cook until thick. Remove from stove and slowly add oil, beating vigorously.

†Use rice flour in Diet 1, cornstarch in Diet 2, and potato flour in Diet 3.

(24)

Purée of Lima Bean Soup

Wash and soak for a few hours two cups of lima beans. Cook in plenty of water salted to taste. When beans are well done, put through a sieve.

Cook small pieces of bacon, crisp. Add enough bacon dripping and crisp fried bacon to purée to make palatable.

(25)

*Lima Bean-Potato Cake and Cookies**

6 tablespoonfuls lima bean flour
 $\frac{3}{4}$ cup potato flour
 5 tablespoonfuls shortening
 $\frac{1}{2}$ cup water
 $\frac{3}{4}$ cup sugar
 $2\frac{1}{2}$ teaspoonfuls baking powder
 $\frac{1}{2}$ teaspoonful vanilla
 $\frac{1}{2}$ teaspoonful lemon extract
 Few grains salt, few drops yellow coloring

Sift dry ingredients, cream fat and sugar, add dry ingredients and water alternately to creamed mixture. Add flavorings and coloring. Put in greased muffin tins and bake in oven at 430° for 30 minutes.

Penoche Frosting

3 cups brown sugar, $\frac{3}{4}$ cup water. Boil sugar and water until soft ball is formed when tested in cold water. Remove from heat, cool, and beat until creamy. An extra tablespoonful of water may be added if necessary for easy spreading. White sugar may be used instead of brown and vanilla or lemon flavoring may be added. Chopped fruit may also be added if desired.

(26)

Carrot Marmalade

5 very large carrots.

4 lemons, squeeze juice and add later, remove all seeds, then grind lemons and carrots together.

10 cups of water, boil all this together for a good half hour, then measure it cup for cup of pulp and sugar.

Boil slowly for an hour or until it jells, as lemons vary some.

*Fat used in recipes for greasing pans or shortening must only be oil or fat specified in the prescribed diet. Baking powder should be Royal or Schilling which contain no egg.

CHAPTER XXXIII

THE ESCALATOR PROGRAM

This is probably the oldest method attempted in the treatment of conditions which might be associated with food idiosyncrasy. It is still part of the routine study of most cases. A sharply restricted diet, with subsequent additions, one food after another, was recommended by Andresen and by Van Leeuwen, and is the procedure followed in the trial and elimination diets, after adequate relief has occurred. This building up with successive single foods might be likened to a staircase, or better, an escalator. One person steps upon the bottom platform. As he is carried upward he is followed by others as successive steps or platforms become available.

Since there is no way except by trial by which we may determine which positive skin reactions are of etiologic significance, the quickest procedure consists in avoidance of all positive reactors unless they are altogether too numerous. As soon as relief is sufficient so that one may recognize an exacerbation of symptoms following an allergenic food, the prohibited foods may be tried out, one after another. Those which fail to produce symptoms may be added permanently. Those which cause symptoms will be eliminated until some subsequent time, when they may again be tried.

Method of addition.—Food additions must not be too rapid. It is not sufficient to try a suspected food once and, in the absence of resultant symptoms, conclude that it is harmless. Symptoms would ensue only in the event the patient was highly allergic and his usual clinical response was of the acute type. Symptoms may be slow in onset. We have mentioned a woman who regularly experiences migraine about 36 hours after eating chocolate. Another with migraine and mucous colitis ate green peas on Sunday. She was known allergic to peas and had avoided them for four or five months, remaining practically symptom-free during this interval. She was in the process of trying out various foods to broaden her diet. From Sunday until Tuesday she felt reasonably well but not quite up to par. On Tuesday she became violently nauseated, vomiting material which she positively asserts was some of the peas eaten two days previously. At the same time she developed an acute mucous colitis. The nausea and colitis persisted for six days. Not having seen the regurgitated material I cannot vouch for the authenticity of its identification, but the forty-eight-hour delay in symptoms in the absence of other recognizable excitants during the interval, is definite. Judging from this case, one should wait at least two days between food additions.

The build-up.—Even two days is not a sufficient interval, since a mild allergic may experience symptoms only following a build-up, with repeated ingestion of the same food on successive days.

Cohen has shown that pollen allergen may continue to circulate, identifiable as such in the blood for upwards of 48 hours. If increments are added at 24-hour intervals cumulative effect may be anticipated. This may be the manner in which the food build-up at last eventuates in symptomatic explosion. At times one must eat the suspected food each day for a week before

developing a breakdown in the allergic equilibrium. Less frequently two weeks will elapse. In one egg case one month was required before temporarily acquired tolerance was exceeded.

The build-up is a difficult type of reaction to study clinically, since the objective methods of study often fail to reveal evidence of sensitization, but I suspect that actually it plays a part in a surprisingly large percentage of patients with chronic food allergy.

It would be a very slow procedure if one were forced to wait an entire month between successive food additions. The majority will react in a shorter interval. One week is usually a safe interval between food additions. During the week the patient should eat the food under study at least once each day. In other words, he should intentionally overload the allergic balance. Even one week intervals make this a rather slow process. With the average case I customarily advise the patient to try successive foods for four-day periods. If at the end of four days the food under consideration has not caused a reappearance of symptoms, the food may be added permanently and taken when desired, while the next food is being tried out during the succeeding four days. This is as short an interval as I have found safe. Even so, occasionally one finds confusion in interpretation of the response, due to the fact that the patient may have tried two low-grade allergens in succession.

This difficulty may be avoided in a measure by having the patient continue with his food diary during the period so that the physician can study an accurate record of what has been eaten on successive days. It may be that two or even three successive foods may have played a part in the final explosion. In this case they must all be tested individually later on, the time interval being lengthened in each case. At the same time it will usually be found that a number of foods may be successfully added at four-day intervals, so that the patient has the pleasure of more rapidly enlarging his diet. Later, after the diet has been made more generous in this way, the two or three foods concerning which there is still uncertainty may be tried, with longer periods for each food.

Duration of reaction. Assuming that a series of added foods causes no return of symptoms, that is, that they are nonallergenic, foods may be added at four-day intervals provided the patient is keeping a food diary so that in the event of symptoms the sequence can be carefully analyzed. If symptoms do ensue, what must be the interval before further foods may be tried? Obviously, one must await complete disappearance of symptoms. How long may symptoms persist following the eating of an allergenic food? They may last for but a few hours, rarely longer than three or four days, but often enough a single ingestion of allergenic food may set off a train of symptoms which may persist for a week or even ten days, in spite of no additional exposure to an excitant during this interval. The woman with migraine and colitis mentioned above had symptoms lasting six days. I have seen this in other cases, especially in migraine, colitis, urticaria and eczema, less frequently in asthma. Whether the train of symptoms lasting through several days may be attributed to the single exposure alone or whether the allergic response upsets the balance to such an extent that nonspecific excitants prolong the attack is not known. The fact remains that a single exposure may result in an attack which may last as long as ten days and which is directly or indirectly attributable to this single exposure.

CHAPTER XXXIV

THE TREATMENT OF FOOD ALLERGY

It is obvious from the foregoing that the treatment of food allergy commences and advances *pari passu* with the continuation studies just described. The trial diet, elimination diet and food addition program all present aspects of one phase of treatment, that of food avoidance.

Other phases which will require consideration include specific hyposensitization, so-called nonspecific protein therapy, other forms of nonspecific therapy based upon allergic concepts, nonallergic therapy, and symptomatic treatment. In nonallergic and symptomatic therapy much depends upon the clinical manifestation. This portion of treatment would be quite different in food asthma from that in migraine or gastrointestinal allergy. The present chapter is devoted rather to the general treatment of allergy to foods, irrespective of the manifestation of the moment.

The specific or semispecific treatment of food allergy as well as other forms of clinical allergy has been based in great measure upon phenomena observed in experimental anaphylaxis. The rationale of the procedure will be more easily followed if we classify them in terms of the earlier experimental investigations.

Antianaphylaxis.—Desensitization.—Otto, and Rosenau and Anderson, later Gay and Southard, observed that if a sensitized animal is reinjected with enough antigen to cause shock but not death, subsequent reinjections, for a time at least, fail to cause reaction. The animal appears to be in a refractory state.

Besredka and Steinhardt (1911) later studied this phenomenon, to which they applied the term antianaphylaxis. They produced the antianaphylactic state in guinea pigs by several specific procedures: (1) intracerebral injection of antigen (horse serum, $\frac{1}{4}$ th cc.) before expiration of the incubation period; (2) intracerebral injection of less than the fatal dose ($\frac{1}{40}$ th to $\frac{1}{450}$ th cc.) after twelve days; (3) intraperitoneal injection of 5 cc. after the incubation period; (4) rectal injection; (5) the administration of shocking doses with the animal deeply narcotized with ether or alcohol.

Besredka first attempted the method of desensitization in clinical use today, that of repeated small doses. The work of Weil and others indicated that production of the antianaphylactic state depended on saturation of tissue antibodies with antigen. Obviously, the more complete the saturation of these sessile antibodies, the more complete will be the desensitization. The larger the desensitizing dose, short of a fatal dose, the better will be the results. If for any reason these large subfatal doses are not applicable, repeated small doses should theoretically gradually saturate the tissue antibodies. Subsequent exposure to large toxic or even fatal doses should cause little reaction.

Antisensitization. Antianaphylaxis or desensitization is to be distinguished from antisensitization or the prevention of the original development of the allergic state. Tuft has summarized examples of antisensitization. A large dose of dog serum injected into a guinea pig with or prior to the first or sensitizing dose of horse serum prevents active sensitization to the latter. Splenectomy,

thyroidectomy, blockade of the reticulo-endothelial system by particulate matter such as India ink, certain infections, as with trypanosomes or tuberculosis, cachexia and vitamin starvation may prevent successful production of the anaphylactic state in animals. Here we are dealing with conditions which exist prior to the attempt to produce allergy with the initial exposure, rather than the removal of the allergic state subsequent to its development or during the course of its development, after the initial exposure. The former is termed antisensitization, the latter desensitization or antianaphylaxis.

Seegal has listed seven factors which particularly influence the development of the anaphylactic state: (1) The species of animal involved; (2) its race; (3) the age of the animal; (4) the diet available; (5) the endocrine function; (6) infection; (7) temperature. Larger amounts of antigen are required to sensitize the dog or rabbit than the guinea pig. The mouse and pigeon are resistant to shock while the rat can be sensitized only when on a deficient diet. Sensitization of monkeys is difficult, and has only recently been accomplished by Caulfield. Fortunately man is another animal difficult to sensitize experimentally. Even within species there is great variation in susceptibility to sensitization. French and German guinea pigs are more resistant than American. While Brazilian pigs are resistant, those from the Argentine are as easily sensitized as those on the Eastern Seaboard of the United States. Seegal has found one family of rats which he could sensitize even though on a normal diet. All other rats studied could be sensitized only when on a deficient diet of bread and water.

Age plays an especially important part in guinea pigs. Very young and very old pigs are sensitized with difficulty.

Diet plays its part. Deficiency in greens renders rabbits and guinea pigs more susceptible. The same occurs with pigeons on a diet of polished rice. Vitamin B deficiency has been found to promote a tendency toward sensitization in rats. "Although it seems established that diet influences the susceptibility of animals to anaphylactic shock, the specific deficiency in the diet which is responsible for this effect needs to be investigated further."

Thyroidectomized guinea pigs are less susceptible to active sensitization although they may be passively sensitized. Adrenalectomized rats are readily sensitized and readily thrown into anaphylactic shock. Partially adrenalectomized guinea pigs are shocked by smaller doses of antigen.

Tuberculous guinea pigs have been found to be more readily sensitized to egg white and timothy pollen than pigs free from infection.

Guinea pigs kept at room temperature are easily sensitized to sheep serum. If kept at a temperature of 6° C. they cannot be sensitized.

A temporary state of anaphylaxis may be produced prior to complete development of the anaphylactic state. Theobald Smith (1904) found that guinea pigs which had received larger doses of serum survived the second or shocking dose more frequently than those which received smaller sensitizing doses. This has since been fully confirmed, that a large sensitizing dose lengthens the time required for the development of the allergic state. Rosenau and Anderson (1906) found the average incubation period in guinea pigs to be twelve days. At the end of twelve days they were allergic. If reinjections were given a few days before the end of this interval and twelve days were allowed to elapse from this second injection, a third or shocking injection found the animals nonresponsive. A longer period than another twelve days had to elapse before they became responsive. The development of sensitization may therefore be de-

layed (a) by large original doses, (b) by repeated doses prior to completion of sensitization. It should be pointed out, however, that even when the animal appears to be in antianaphylaxis, especially when a second dose has been given a short time prior to the complete establishment of sensitization, the animal will still react, with shock, even death, provided the shocking dose is increased to many times that which normally produces death. Weil has spoken of this as *masked anaphylaxis*.

Clinical Application

Antisensitization.—In clinical allergy the subject is seen after the development of sensitization and we are not in a position to attempt procedures that would fall in the category of antisensitization. However, it seems to the writer within the realm of probability that many of the processes which nature employs in the prevention of sensitization may be found to be correlated with the experimental observations on antisensitization. We have mentioned that simultaneous sensitizing injections of horse and dog serum in differing dosages result in protection against sensitization with the lesser antigen. Some similar phenomenon may explain why we do not become universally allergic to all allergens; why with apparently similar exposure to wheat, egg and milk some will become allergic to one but not to another. This phenomenon of protection against multiple simultaneous sensitization has its analogy in infectious diseases, especially those of childhood, where the existence of one active disease appears to temporarily preclude the development of another. The possible rarity of multiple simultaneous sensitization is not to be confused with the obvious frequency of multiple successive sensitizations. By the same token we must realize that specific desensitization against one antigen does not desensitize against others. If a guinea pig sensitized to horse serum and egg white is shocked with a sublethal dose of horse serum, he will become anti-anaphylactic to the latter but will still react with shock to a shocking dose of egg white. The amount of reinjected egg white must, it is true, be slightly larger than that which would otherwise have shocked the animal, but the difference in dosage is not great.

Antisensitization may eventually be found to play a part in the observed fact that minor allergies do not become sensitized to the substances to which they are chronically exposed. If an animal is given a sensitizing dose of foreign protein and is reinjected frequently thereafter, at intervals shorter than the twelve days required for completion of sensitization, the animal will not respond with evidence of anaphylaxis, at least until some time after the injections have been discontinued. This applies in the guinea pig, not so in the rabbit, in which animal the Arthus phenomenon becomes apparent.

Constitutional states such as cachexia, vitamin deficiency, endocrine disturbance or systemic infections, conditions discussed above under antisensitization, may possibly play a part in the predisposition of an individual to become allergic. The factor of race was discussed in the introductory chapter. There is evidence that some races resist the development of sensitization more than others. This is seen in different species of animals and even among members of the same species. Sulzberger and Simon reported differences in the ease of sensitization of Boston and New York guinea pigs to arsenical preparations. Victor Vaughan (1913) remarked on the fact that French guinea pigs are less easily sensitized than American.

There is not much that we can do today in a therapeutic way in the application of antisensitization. The need for further knowledge in this field is obvious. First, it involves the prevention of development of the allergic state in individuals who are known to be predisposed by heredity. Second, it involves appropriate treatment of the individual who has become sensitized to a certain allergen, with a view to preventing the development of new sensitizations. This is a fundamental program of utmost importance, the solution of which has not yet been reached. Adequate accomplishment in this field must await a truer understanding of the basic mechanism of allergy and recognition of new experimental phenomena which can be applied to the desired end. At present we can apply only the most general principles of antisensitization.

Desensitization.—Specific desensitization has been employed in food allergy as well as in other forms, particularly inhalant allergy and serum sensitization. It has been decidedly less effective in the first. In this connection a phrase employed in clinical allergy, based upon the Ehrlich side chain theory, is very frequently misused. This is the term antibody exhaustion. Desensitization with repeated small but increasing amounts of antigen in accordance with the Besredka technic does not produce antibody exhaustion. This has been shown experimentally and is easily observed clinically where prolonged desensitization does not cause disappearance of reagin. When protection is adequate as indicated by relief of symptoms, the reaginic antibody can be shown by passive transfer to be present in the blood in large quantities. Here we are not dealing with antibody exhaustion. The explanation may be the formation of the “blocking antibody” which results from treatment and is believed to unite with the antigen, thus preventing the union of antigen and reagin. Treatment may actually increase the reagin and thereby actually increase the sensitivity of the patient, but the blocking antibody, if sufficient in amount, will serve to protect the cells and thereby prevent the development of symptoms. If this theory is correct, specific treatment has its value as an immunizing process. Loveless finds that there is at least a crude relationship between the “blocking antibody” titer and the clinical protection of the patient.

Hypodermic medication. It was but natural with the evidence accumulated in experimental anaphylaxis and the good results from parenteral medication in pollen allergy, that hypodermic food desensitization should be attempted. It is surprising that none of the investigators who have attempted hypodermic desensitization in food allergy have reported consistently favorable results. Early investigators in this field were Cooke (1922), Campbell (1926), Rackemann (1928). The method is rarely used. When it is employed the initial dose should be very small and may be determined in a manner similar to that employed in desensitization with inhalant allergens. Scratch or endermal tests are first made with serial dilutions of the food extract, each successive dilution being ten times greater than the former. The endermal dilution which just fails to react is employed for the beginning of desensitization. If scratch tests were done, the first desensitization solution is 100 times more dilute than the scratch solution which just fails to produce a reaction. Injections are given at least twice weekly, with gradually increasing concentration as in preseasonal pollen desensitization, until a concentration is reached at which the patient finds he can ingest the offending food without resulting symptoms or at which tolerance fails and the injections cause an increase in symptoms. In the latter case the dose is reduced somewhat to where it no longer causes symptoms and is thereafter maintained at that level.

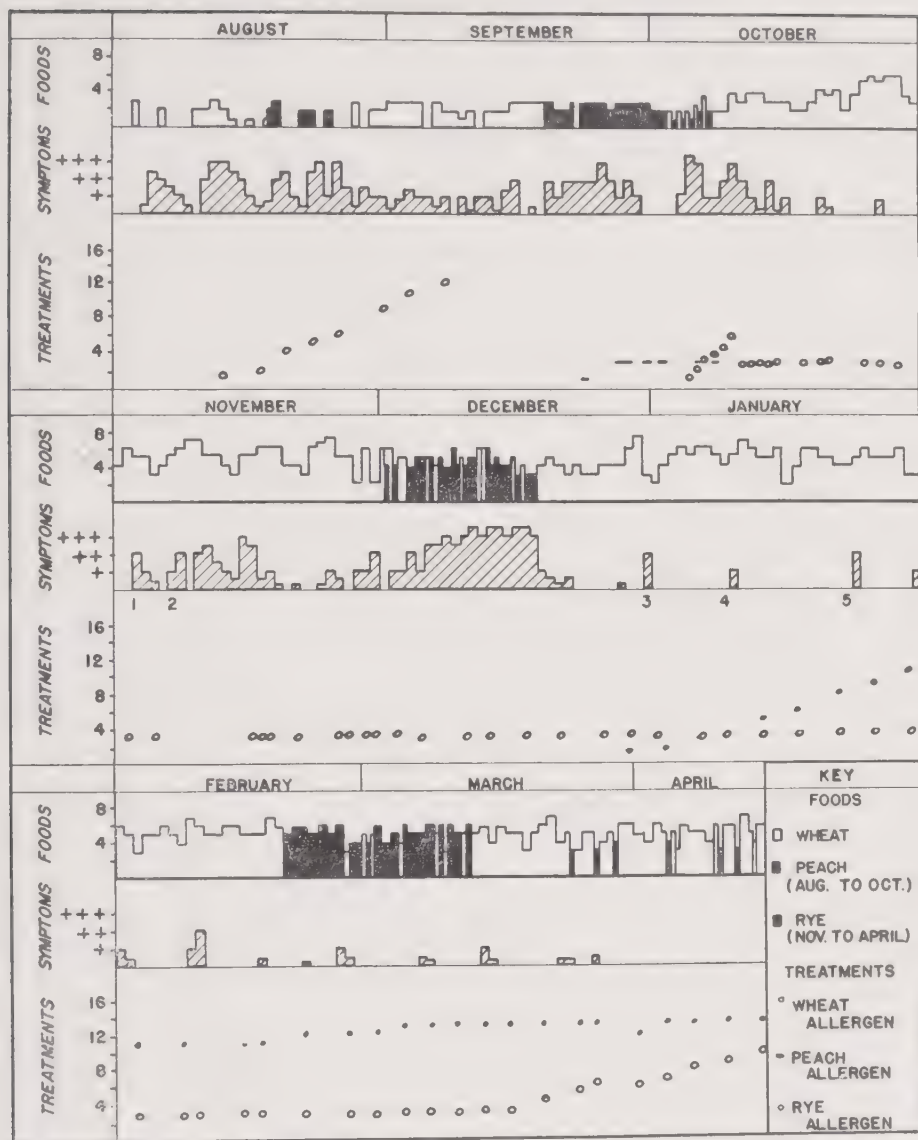


Fig. 68.—Cocibal hyposensitization. A long term daily summary of response to subcutaneous small dosage food hyposensitization using the principles of coseasonal pollen therapy. During August, wheat and peaches were eaten and allergic symptoms (asthma and rhinitis) were pronounced. Wheat hyposensitization was commenced. In September, although more wheat was eaten, symptoms were less pronounced. September 18, wheat was eliminated from the diet and peaches were substituted. Symptoms became more pronounced. With peach hyposensitization the subject was relieved, early in October, even though he continued to eat peaches.

October 3, wheat was again added, approximately one month after wheat hyposensitization had been discontinued. Symptoms returned at once. Wheat injections were recommenced, with rapid symptom improvement. Low dosage (0.3 c.c. of 1:10,000 dilution) was found adequate, even though the amount of wheat eaten was steadily increased. With discontinuance of treatment, November 7, symptoms returned, again to be relieved when wheat injections were recommenced.

December 1, with wheat still in the diet, rye was added. Symptoms became pronounced. December 18 rye was discontinued, with rapid relief. Wheat ingestion and wheat desensitization were continued. The subject then started a period of two months with hyposensitization to wheat and rye, at the end of which (February 20) he again added rye to the diet. Symptoms did not recur. From March 12 to the end of the study he ate wheat and rye indiscriminately, continuing with hyposensitization to these two foods and remaining practically free from symptoms. In this chart exacerbations are readily traced to their causes and symptomatic improvement in the second half of the study is readily seen.

Numbered episodes (November-January) are explained as follows. 1, Ate chocolate the previous evening; 2, ate tomatoes and drank coffee the previous day; 3, exposed to orris root at barber shop; 4, peaches the preceding day; 5, coffee and chocolate the preceding day. Subject was allergic to all of these.

Endermal desensitization has also been attempted, likewise with no very satisfactory results and with an observed greater tendency toward constitutional reactions.

McLarand, in my clinic, has recently obtained promising results from small dosage hypodermic hyposensitization to foods, on a basis similar to that followed in small dosage coseasonal pollen therapy. Injections are given twice weekly for an indefinite period as long as the patient continues to eat the allergenic food. No attempt is made to increase the concentration over that first selected and described above (see Fig. 68).

Parenteral food desensitization is not generally recommended at present except in those cases in which the food element causes symptoms from inhalation. This applies, for example, with bakers and housewives who develop asthma following inhalation of flour dust. Here the results are often as satisfactory as in other forms of inhalant allergy. We have also obtained quite satisfactory results in some cases of dermatitis associated with allergy to the cereal grains, chiefly persons who handle the various flours, and who on account of occupation cannot completely avoid them. These have been cases of atopic eczema, presenting the picture of neurodermatitis, but I have also seen distinct improvement in cases of apparent contact dermatitis, with exudation, due to contact with cereal allergens. However, it should be borne in mind that even though the picture is that of contact dermatitis, reagin to the etiologic agent was demonstrated in the patient's blood.

Oral desensitization. Here, the procedure consists in starting with extremely minute quantities of the offending allergen by mouth and gradually increasing the quantity. One may look upon this as comparable to Besredka's fractional desensitization with gradual saturation of fixed tissue antibody. Or one may look upon it as comparable to the therapeutic procedure in physical allergy, acclimatization of the tissues to increasing quantities of the deleterious environmental agent.

The possibility of oral desensitization was demonstrated early in experimental anaphylaxis by Wells who found that guinea pigs bred from mothers fed on oats became allergic to oats if this food was eliminated from their diet. If they were fed oats they ceased to show evidence of sensitization. This observation demonstrated (1) sensitization acquired in utero and (2) desensitization following long continued exposure, even by mouth, comparable to the antianaphylaxis observed by Otto following repeated injections of horse serum.

Schofield (1908) first reported successful treatment of egg allergy after oral administration of minute amounts. Schloss (1912) similarly relieved symptoms from egg sensitization by feeding increasing doses of ovomucoid. Talbot (1914), Walker (1917), Park (1920) and Stuart and Farnham (1926) reported similar results.

Finklestein (1905) proposed treatment of milk idiosyncrasy in nurslings by the administration of two or three drops of milk daily, with subsequent increase. Finizio (1911) reported good results from oral milk desensitization. This method was used in food allergy by La Roche, Richet and Saint Girons (1919).

The results of oral desensitization, like those following parenteral treatment, have not been startlingly good. Even when success is achieved, a long time is required (from three to eight months in Schofield's and Schloss' cases). Keston, Waters and Hopkins have revived interest in oral desensitization to

those foods the avoidance of which is difficult or complicated. They have outlined a program for treatment of sensitization to egg, wheat, milk, chocolate, tomato and orange.

The patient is started with an extremely small amount of the antigen, and every four days the quantity is increased in a regularly prescribed schedule. Black has reported very good results with this method. He has modified the original method slightly, and states that approximately three of four wheat-sensitive patients have been able to go back to the normal use of wheat.

Overdosage may occur with this method as it does with parenteral therapy. If the patient's symptoms recur, the use of the schedule should be stopped for five or six days. If symptoms clear up, it may be assumed that the dosage was being increased too rapidly and the patient drops back twelve to sixteen days on the schedule. If stopping the schedule does not bring about the subsidence of symptoms, it may be assumed that they are not due to overdosage, and another explanation should be sought.

METHOD OF DESENSITIZATION TO WHEAT

Use uncooked wheat flour. Add a small amount of water to the flour to wet it and avoid lumps. Stir into the water thoroughly. Discard all but enough to insure you having four teaspoonfuls. Put this into the refrigerator and use a teaspoonful once a day for four days. It may be taken at any time of day and with other food if desired. Place a check mark opposite the proper dilution each time a dose is taken to avoid mistakes in dosage.

Mix $\frac{1}{2}$ teaspoon flour with 1 quart water
 Mix 1 teaspoon flour with $1\frac{1}{2}$ quarts water
 Mix 1 teaspoon flour with 1 quart water
 Mix 1 teaspoon flour with 3 cups water
 Mix 1 teaspoon flour with 1 pint water
 Mix 1 teaspoon flour with $1\frac{1}{2}$ cups water
 Mix 1 teaspoon flour with 1 cup water
 Mix 1 teaspoon flour with $\frac{3}{4}$ cup water
 Mix 1 teaspoon flour with $\frac{1}{2}$ cup water
 Mix $\frac{1}{2}$ teaspoon flour with 3 tablespoons water
 Mix 1 teaspoon flour with $\frac{1}{4}$ cup water
 Mix 1 teaspoon flour with 3 tablespoons water
 Mix 1 teaspoon flour with 2 tablespoons water
 Mix 2 teaspoons flour with 3 tablespoons water
 Mix 3 teaspoons flour with 3 tablespoons water
 Mix 4 teaspoons flour with 3 tablespoons water
 Mix 6 teaspoons flour with 3 tablespoons water
 Mix 6 teaspoons flour with 6 teaspoons water
 Eat $\frac{1}{8}$ slice of bread daily for 2 days
 Eat $\frac{1}{4}$ slice of bread daily for 2 days
 Eat $\frac{1}{2}$ slice of bread daily for 2 days
 Eat 1 slice of bread daily for 2 days
 Eat $1\frac{1}{2}$ slices of bread daily for 2 days
 Eat 2 slices of bread daily for 2 days
 After this eat some wheat product daily.

METHOD OF DESENSITIZATION TO MILK

Add the prescribed amount of milk to the water and stir thoroughly. Discard all but enough to insure you having four teaspoonfuls. Put this into the refrigerator and use one teaspoonful once a day for four days. It may be taken at any time of day and with other food if desired. Place a check mark opposite the proper line each time a dose is taken to avoid mistakes in dosage.

Mix 1 teaspoon milk with 1 quart water
 Mix 1 tablespoon milk with 2 quarts water
 Mix 1 teaspoon milk with 1 pint water
 Mix 1 tablespoon milk with 1 quart water
 Mix 1 teaspoon milk with 1 cup water
 Mix 1 tablespoon milk with 1 pint water
 Mix 1 teaspoon milk with $\frac{1}{2}$ cup water
 Mix 1 tablespoon milk with 1 cup water
 Mix 1 teaspoon milk with $\frac{1}{4}$ cup water

Mix 1 tablespoon milk with $\frac{1}{2}$ cup water
 Mix 1 teaspoon milk with 2 tablespoons water
 Mix 1 tablespoon milk with $\frac{1}{4}$ cup water
 Mix 1 teaspoon milk with 1 tablespoon water
 Mix 1 tablespoon milk with 2 tablespoons water
 Mix 2 teaspoons milk with 1 tablespoon water
 Take 1 teaspoon milk
 Take $1\frac{1}{2}$ teaspoons milk
 Take 2 teaspoons milk
 Take 3 teaspoons milk
 Take 4 teaspoons milk
 Take 2 tablespoons milk
 Take 3 tablespoons milk
 Take $\frac{1}{4}$ cup milk
 Take $\frac{1}{3}$ cup milk
 Take $\frac{1}{2}$ cup milk
 Take $\frac{2}{3}$ cup milk
 Take 1 cup milk
 Take a little more each day until two cups are
 being taken daily.

METHOD OF DESENSITIZATION TO EGG

Beat an egg sufficiently to mix white and yolk and add the prescribed amount of egg to the specified amount of water. Stir thoroughly. Discard all but enough to insure you having four teaspoonfuls. Put this into the refrigerator and use one teaspoonful once a day for four days. It may be taken at any time of day and with other food if desired. Place a check mark opposite the proper line each time a dose is taken to avoid mistakes in dosage.

Mix $\frac{1}{4}$ teaspoon egg with 8 quarts water
 Mix $\frac{1}{4}$ teaspoon egg with 6 quarts water
 Mix $\frac{1}{4}$ teaspoon egg with 4 quarts water
 Mix $\frac{1}{4}$ teaspoon egg with 3 quarts water
 Mix $\frac{1}{4}$ teaspoon egg with 2 quarts water
 Mix $\frac{1}{4}$ teaspoon egg with 3 pints water
 Mix $\frac{1}{2}$ teaspoon egg with 2 quarts water
 Mix $\frac{1}{2}$ teaspoon egg with 3 pints water
 Mix 1 teaspoon egg with 2 quarts water
 Mix 1 teaspoon egg with 3 pints water
 Mix 1 teaspoon egg with 1 quart water
 Mix 2 teaspoons egg with 3 pints water
 Mix 1 teaspoon egg with 1 pint water
 Mix 2 teaspoons egg with $1\frac{1}{2}$ pints water
 Mix 1 teaspoon egg with 1 cup water
 Mix 2 teaspoons egg with $1\frac{1}{2}$ cups water
 Mix 1 teaspoon egg with $\frac{1}{2}$ cup water
 Mix 2 teaspoons egg with $\frac{3}{4}$ cup water
 Mix 1 teaspoon egg with $\frac{1}{4}$ cup water
 Mix 1 teaspoon egg with 3 tablespoons water
 Mix 1 teaspoon egg with 2 tablespoons water
 Mix 2 teaspoons egg with 3 tablespoons water
 Mix 1 teaspoon egg with 1 tablespoon water
 Mix 4 teaspoons egg with 3 tablespoons water
 Mix 2 teaspoons egg with 1 tablespoon water
 Take 1 teaspoon of egg
 Take $1\frac{1}{2}$ teaspoons of egg
 Take 2 teaspoons of egg
 Take 3 teaspoons of egg
 Take 4 teaspoons of egg
 Take $\frac{1}{2}$ egg
 Take $\frac{3}{4}$ egg
 Take a whole egg
 After this eat at least one egg every few days.

Specific peptone therapy—Skeptophylaxis. It became apparent that peptone as a nonspecific desensitizing agent was generally unsuccessful. Further more the rationale of the procedure ceased to exist when it was shown that Biedl and Kraus' original theory of the interrelationship between peptone shock and anaphylactic shock was incorrect. More recent investigations of oral peptone treatment in food allergy have been predicated upon a different premise, a supposed specificity of the procedure.

Auld, and Vallery-Radot and Blamoutier used combined peptones derived from various foods of animal and vegetable origin. This was also recommended by La Roche, Richet and Saint Girons who employed mixed peptones from meat, milk and fish.

Luithlen appears to have first stressed the idea of specificity in peptone desensitization. After his death Urbach continued the investigation. According to the latter skeptophylaxis is a form of antianaphylaxis attained by the administration of the allergen in minimal amounts 45 to 60 minutes prior to each meal. The procedure as developed by Luithlen and Urbach is basically similar to the earlier French method of feeding small quantities of the food prior to the regular meal, with the idea that temporary partial desensitization would occur and that the patient could then eat the food at meal time with impunity.

Urbach designated his specific peptone, propeptan. Peptones were made from 28 different foods, "taking great care to preserve the specificity of the peptone by not going too far with whatever chemical process was used in breaking down the protein." According to the theory we are dealing with a substance which is still antigenic but less highly so than the original source material, a substance which may be taken 45 minutes prior to the ingestion of the original material, and which will produce a temporary state of anti-anaphylaxis.

Urbach then prescribed a diet containing only foods for which propeptans are available. These are administered in tablet form prior to the ingestion of each particular food. Since according to the author they are active only on an empty stomach, meals are spaced four hours apart. If on this diet with propeptan treatment the patient is relieved after three days then one after another of the propeptans are omitted on successive days. When symptoms return they may be attributed to the last propeptan omission and that food is considered allergenic. In this way the various allergenic foods are determined. Following the preliminary study the patient is again placed on the full meal of 28 foods. Now, only those propeptans are to be taken the omission of which was followed by symptoms. The patient stays on this program which includes the allergenic foods and their propeptans, for from 14 to 30 days, after which desensitization is said to be complete. Thereafter, propeptans may be omitted but the foods are continued.

Obviously, the success of this procedure depends upon the correctness of the theory. Can a protein be partially digested toward the peptone stage and remain partially antigenic? Will such a modified antigen protect against exposure to the unaltered allergen 45 minutes later? Will repeated administration of this altered allergen synchronously with repeated contact with the whole allergen permanently desensitize an individual within thirty days or within any length of time?

Although Urbach in his early investigations reported the disappearance of a positive skin reaction 45 minutes after propeptan ingestion, he later stated that the disappearance of a positive cutaneous response was not necessary for good results. Both Rowe and Vaughan found that in the cases studied the skin reaction did not become negative following propeptan therapy. Of course this does not mitigate against possible value of the method since the same situation holds in pollen allergy, in which one may be entirely adequately relieved even though the skin reaction is still strongly positive.

The writer undertook propeptan therapy in a small series of food allergies, following the procedure outlined by Urbach but was unable to demonstrate definite benefit. Rowe in a much larger series reached the same conclusion. Bray reached similar conclusions. Cleveland White failed to observe benefit in cases with acneiform dermatitis. It should be noted, however, that Urbach's conclusions were reached chiefly from the treatment of food dermatoses, presumably atopic eczema. So far as I know no one in this country has undertaken a comprehensive study of the effect of propeptan in this particular type of food allergy.

Conflicting conclusions.—Summarizing the discussion of peptone therapy, we may say that in general good results have been reported by responsible observers on the European Continent but that the great majority of those in North America have failed to achieve similar success. One is inclined to conclude that one group must be right and the other wrong. This may be so. Certain it is that in the esoteric cult of students of anaphylaxis and allergy many false hopes have been raised, usually based upon the clinical application of some theory which is later shown fallacious. We have seen this in the discussion of peptone shock. Another outstanding example is the earliest specific remedy, pollantin, introduced by Dunbar on the false premise that hay fever is caused by a toxin secreted by the pollen. Nevertheless pollantin was enthusiastically received and widely used.

We must recognize another possible explanation. Just as guinea pigs vary in susceptibility to sensitization, the French, German and Brazilian animals being distinctly less susceptible than those from the Argentine and the eastern United States, so also as we have observed, there is a variation in racial susceptibility among human beings. It is not impossible that a therapeutic procedure which would be efficacious with one group in one part of the world would be unsuccessful with a group elsewhere.

Nevertheless I feel that we are on safe ground in saying that peptone therapy, specific or nonspecific, is not the solution to food allergy, anywhere.

Rectal desensitization. In the discussion of antianaphylaxis we stated that Besredka accomplished this by rectal instillation of the antigen. In the preceding section we have raised three questions concerning the accuracy of Urbach's theory. The first was concerned with the continued allergenic activity of the changed allergen. The rectal administration of the unchanged allergen would obviate this question. The others would remain still to be answered. Another question would arise. Although inarticulate animals can be protected against fatal anaphylactic shock following the rectal administration of the antigen, would human beings with various symptoms such as the pain of migraine or colitis be able to receive the allergen through this route without exaggeration of their symptoms?

This is a possible therapeutic procedure which might merit attention. I know of only one instance in which it has been applied in food allergy. Victor C. Vaughan, Jr. (1913), soon after the publication of Besredka's investigations, relieved a woman with gastrointestinal allergy due to chicken by means of daily rectal instillations of chicken broth following cleansing enemas. This study has not previously been reported.

Smyth and Stallings have shown by passive transfer studies that egg white may be absorbed from the colon of normal infants. Infants aged 3 to 7 days were passively sensitized endermally with serum from an egg white allergic

The test solution, 15 cc. of egg white in 300 cc. of distilled water, Seitz filtered, was instilled into the rectum in 2 to 3 cc. doses at two or three minute intervals until a total of 20 cc. was given. Positive reactions appeared at the passively sensitized skin sites within twenty to sixty minutes, indicating absorption of the antigen through the colonic mucosa and its transportation through the blood to the sensitized areas.



Fig. 69.—The interaction of multiple etiologic factors. Although some allergies respond to inhalant hyposensitization only, or to dietary restrictions, or to the avoidance of contact substances, many do not do well until two or more of these, or other factors, are controlled. This child's dermatitis improved with the avoidance of egg but did not clear up until the mattress was covered, scented talcum powder was discontinued, and she was desensitized to theorris root and dust extract.

Denaturization of foods.—Attempts to change the antigenic activity of a food such as milk by treatment at high temperatures, desiccation, etc., does not fall in the category of desensitization. This will therefore be discussed under the individual foods.

Other therapeutic procedures.—Nonspecific protein therapy such as auto-hemotherapy; nonspecific therapy based upon allergic concepts, such as the use of calcium, ephedrin, adrenalin, etc.; nonallergic therapy, which includes general dietary procedures, vitamins, measures designed to promote digestion or elimination and to improve the general health; and symptomatic treatment are all very much the same in food allergy and the other allergic manifestations and will be discussed elsewhere.

Summary

The most successful therapeutic program in food allergy consists in (a) searching for and finding the offending allergens, (b) their elimination from the diet, (c) the providing of an adequate dietary program with substitute foods, (d) food additions as rapidly as the patient's tolerance will permit. When



Fig. 70.—Difficulty of controlling excitants. This child, allergic to a number of foods, to his own house dust, and to several animal danders lived on a small farm where it was impossible for him to avoid the excitants. Three or four months' sojourn in a hospital always produced near-cure, but soon after his return home symptoms invariably returned, as severe as ever. His parents found it financially impossible to provide an adequate change in the home environment.

avoidance is impossible, desensitization either orally or parenterally may be attempted although this method is usually not as successful. There is evidence that the natural tendency is toward loss of sensitization provided the tissue response is not repeatedly restimulated by recurrent exposure to the allergen. After sensitization has been lost, following avoidance, the patient often finds that he can again eat the offending food in moderation. The period of avoidance varies from a few months to many years. The writer found in a series of migraine cases that the average period was four and one half years. Some persons appear to retain their sensitization for an indefinite period (at least 12 years in my experience).

One, mildly sensitized, can often tolerate the food in small quantities or when taken at infrequent intervals. Thus a wheat allergic may tolerate bread once or twice weekly but not daily, or once daily but not at each meal. It follows that, when tolerance has been re-established by avoidance, and the



Fig. 71.—The importance of differential diagnosis. Eczema of the nipple and areola closely resembling Paget's disease. The lesion cleared up entirely with dietary restrictions. It is as important for the allergist not to overlook Paget's disease as it is for others to realize the possibility of an allergic etiology.

food is again being eaten, it should be taken in decided moderation. Otherwise, active sensitization may recur. This does not apply during the escalator program, where larger quantities are intentionally prescribed, to determine definitely the presence or absence of sensitization.

Not all positively reacting foods cause trouble. In our experience on an average about half are found to be truly allergenic and productive of symptoms.

In America, allergic diagnosis and treatment are based primarily on the conception of specificity. The primary search is for the specific excitant. In France less attention is paid to this, more to nonspecific therapy and the improving of the patient's general health. As Richet has suggested to the writer, in America we pay attention to the excitant while in France interest is primarily in the terrain.

PART VI

FOOD ALLERGENS

*What's one man's poison, signor,
Is another's meat or drink.*

—BEAUMONT AND FLETCHER.

Love's Cure
Act III, Scene 2

CHAPTER XXXV

FOOD ALLERGENS AND THEIR AVOIDANCE

Experience has shown that almost any food may be potentially allergenic. The major allergic becomes sensitized to the commoner foods. Both major and minor allergies may become atopic to occasional, even rare food substances. The nature of the food appears to play some part since with presumably equal or comparable degrees or periods of exposure there are undoubtedly certain foods which are more likely to cause symptoms than others. Foods eaten rarely in one country may be used as substitutes for commoner foods to which the individual has become sensitized. There is no assurance that he will not later become allergic to the substitute foods. As a matter of fact, some of the evidence suggests that one is especially likely to become sensitized following exposure to a new or strange potential allergen to which the body has not yet become adjusted or "acclimatized." Nevertheless, until such secondary sensitization does occur, it is a logical procedure to recommend previously unused or little used foods as substitutes.

Since it seems desirable that the student of food allergy be versed in the biologic characteristics of the various foods and their interrelationships, the order of presentation will be botanical.

Foods which are occasionally used may be derived from surprisingly low forms of plant life. Probably the lowest is from the algae. As far as human food is concerned, this is limited almost entirely to the seaweeds. The fungi contribute mushrooms and kindred edible plants. Fungi constitute an edible portion of several varieties of cheeses. Yeasts and fungi are constituents of fermented foods and beverages. Yeast may be eaten alone. Bacteria constitute an undesired nutritional element much more often than the reverse, although the acidophilus bacillus is a desirable ingredient of buttermilk and is at times intentionally added to milk, thereby becoming a food element.

Moss rarely becomes a food except in Iceland and Norway where the "Iceland Moss," a moss-like lichen, is used as a filler, comparable to agar. It has very little food value. Fern plants are not used as foods.

The highest evolutionary plants are the "seed plants." These spermatophytes include two general groups, the Gymnospermae and the Angiospermae. The former includes cone bearing plants such as pines, spruces, firs, cedars,

hemlocks and junipers, while the latter include all of the common crop plants. Members of the Gymnospermae rarely contribute to our diet, but extracts, especially of the oils, are sometimes used medicinally, in beverages, and to impart flavor to foods. Thus, the juniper berry is too pungent to be eaten raw but it gives a nice flavor to corned beef and is used in Germany for smoking hams. It is also employed at times in the flavoring of gin.

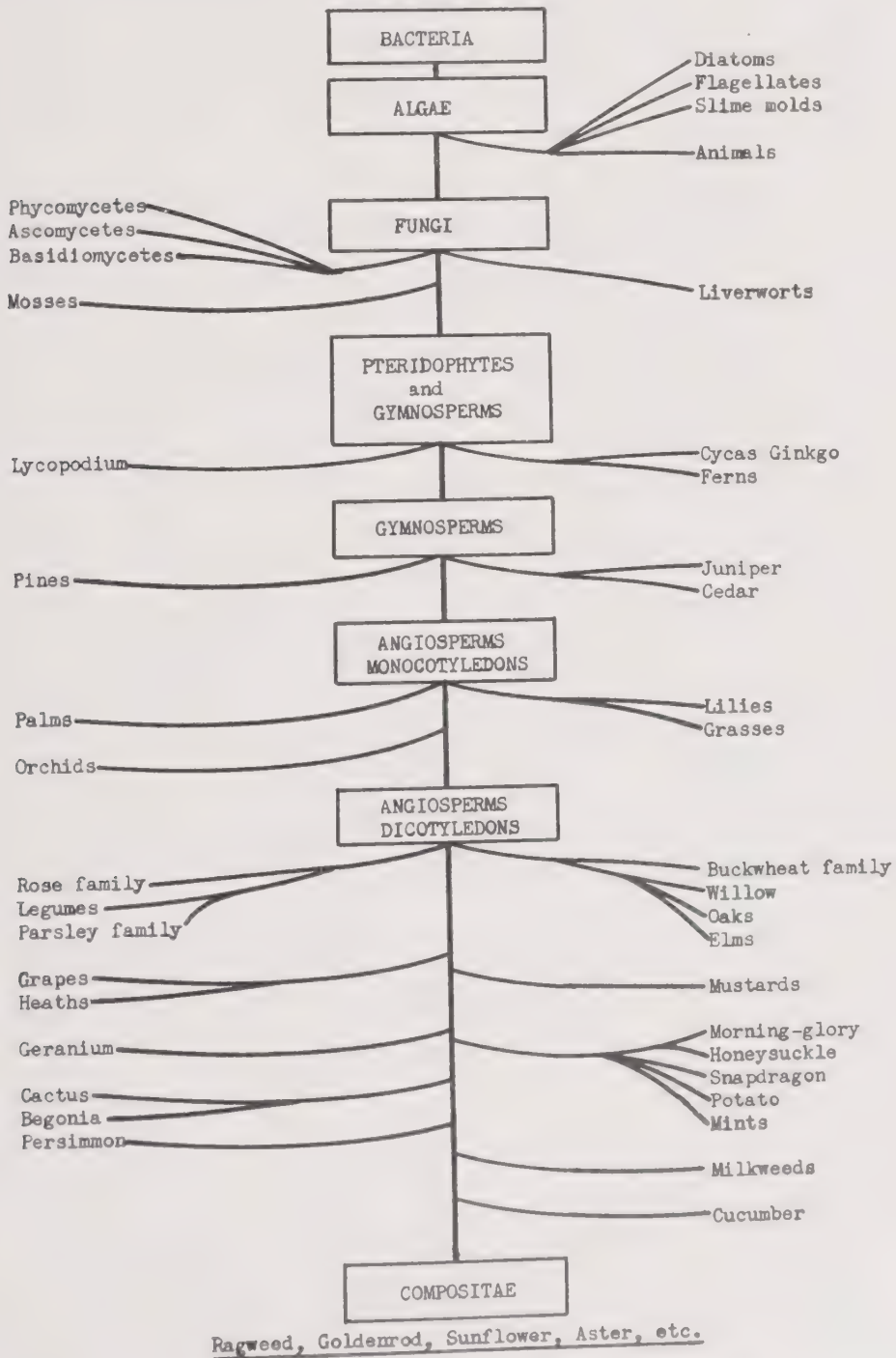


Fig. 72.—Outline of plant evolution from bacteria to the composites. Gymnosperms "naked seeds," are of lower evolutionary development than angiosperms, "seeds in vessels." Dicotyledons represent higher groups than monocotyledons. The Compositae are the highest group among the dicotyledons. The chart includes only some of the commoner examples.

The Angiospermae, the common flowering plants, are again divided into two groups, the monocotyledons and dicotyledons. As is true throughout botanical classification, the differentiation depends upon differences in manner of reproduction or in the characteristics of the reproductive tissues. The cotyledon is the fleshy storage organ in the seed which furnishes nourishment while it is sprouting, that is until the root has been able to grow sufficiently down into the soil, and the first leaves can grow upward enough so that the developing plant can take over the manufacture of its own food by photosynthesis and root absorption. The cotyledon, therefore, disappears in the growing plant after it has served its temporary function. A familiar dicotyledonous seed is the peanut in which the two symmetrical cotyledons represent the major bulk of the nut.



Fig. 73.—Dicotyledons. The cowpea illustrates well what is meant by dicotyledons. Two storage organs provide sufficient nourishment for the seed to sprout, putting out its roots and the two primary leaves. In the monocotyledon, represented by the grain of corn, there is but one storage vessel.

Monocotyledonous plants have but a single storage organ attached to the latent plant bud. Corn is a familiar example. The commoner monocotyledonous foods include the cereal grains and members of the lily family such as onion and asparagus.

EDIBLE PLANTS

Algae—Seaweeds

Agar-agar.—A Japanese seaweed used chiefly in the textile, silk and other industries. It is occasionally employed to thicken jams, jellies and ice cream. Medicinally it is employed to increase fecal bulk. The writer has observed one patient allergic to iodine who was unable to take preparations containing agar.

Irish moss.—Also known as carrageen or pearl moss. A small edible seaweed found along the coast of the British Isles and eastern shores of the northern United States and Canada. In this country it is obtained principally from New Hampshire and Massachusetts. Carrageen is used in the preparation of blanc-mange, occasionally in jellies and in the clarifying of malt beverages. Like agar its value lies in its gelatinous property. Its nutritive value is negligible.

Fungi

Mushroom.—The mushroom is the fruit of a fungus, the mycelium of which remains underground. We may look upon it not as the fungus itself but as its fruit. There are at least twelve varieties of edible mushroom. This plant is rather frequently allergenic. Since it is often used to flavor sauces, gravies, and soups it sometimes appears unexpectedly in the diet.

Truffle.—The truffle, like the potato, grows beneath ground but has neither a root nor upper portion. It grows chiefly in France, also in Germany, Italy, Spain, England, and California. It possesses a pleasant, characteristic odor and is located by the farmer, beneath the surface of the ground, with the aid of trained hogs and dogs. They are guided to the truffle by the scent. Truffles constitute the black substance observed in *paté de foie gras* and are occasionally seen in sausage, especially liver sausage. They may be obtained in cans and, like mushrooms, may be used as flavoring, by allergies who are not sensitized to them but must avoid certain other flavoring substances.

Puffballs.—These resemble the mushroom in properties and flavor. They are quite common in the United States but are rarely used as food.

Molds.—These are only incidental food constituents, being used chiefly in the manufacture of certain cheeses and, in Japan, fermented beverages. (See cheese, also chapter on molds and yeasts.)

Yeast.—This member of the fungus family is used in the manufacture of fermented beverages, some cheeses, and in the preparation of raised bread and griddle cakes, especially in the old-fashioned buckwheat cakes where some of the dough is held over from one day to the next for the purpose of seeding the new batch.

Taub has described a case of asthma, in a young boy, which was found to be due to atopy to yeast, with symptoms following its ingestion. The boy reacted positively to Fleischmann's yeast, baker's, distiller's, brewer's, lactofermenting and lager beer yeast. These reactions were obtained both on direct testing and on passive transfer. The omission of yeast products from the diet relieved his asthma.

Fleischmann's yeast cakes contain no wheat or wheat products. The small cakes contain not over 5 per cent tapioca flour, to better preserve the yeast during transportation and use and a small amount of carotene in cottonseed oil. The Fleischmann pound cake of regular bakers' yeast is 100 per cent pure yeast and according to the manufacturer, contains no cereal of any kind.

The small cakes for home use are irradiated to produce vitamin D. They also contain a small amount of carotene in cottonseed oil, to increase the vitamin A content. Neither vitamin A nor vitamin D is added in the pound yeast.

Unleavened bread contains no yeast. This is obtainable at delicatessens as *matzoth*, the bread customarily eaten by the Hebrews during the period of the Passover. It is really a wheat wafer.

The Gymnosperms

Pine nut.—*Pinus*.—Also known as Indian nut, pignon, pinon, and pignolia. This is the seed of the pine tree, in several varieties of which it is edible. This applies to the Pinon Pine of the southwestern states and Mexico, Nepal Pine of the Himalayas, the Stone Pine of western North America. The cones are heated to spread the scales, after which the nuts may be easily removed. They are small, narrow, rather lozenge shaped, although those of Brazil and Chili may be as much as two inches long. The taste is not unpleasant, being rather a cross between that of the almond and of turpentine. The nut is used in confectionery and pastry and may be eaten raw, roasted, and salted. In the Himalayas the seed is stored for winter use and forms a staple article of diet. It is ground and mixed with flour.

The Angiosperms

THE MONOCOTYLEDONS

Cereal Grains

Wheat.—*Triticum sativum*.—The origin of wheat is not definitely known but it appears to have been developed originally from the wild grasses of Asia Minor or Egypt or around the shores of the Caspian Sea. It was introduced into China about 3,000 B.C. and was described as being present in Egypt about 2440 B.C. That wheat was cultivated in Europe prior to the period of written history is indicated by its recovery from the habitations of the Lake Dwellers in Switzerland. In France, during the reign of Charlemagne, wheat was looked upon as the most valuable of the grains. It was the most expensive, with rye, barley and oats costing successively less. Owing to the climate and the character of the soil, wheat appears not to have been cultivated by the early Britons. Its culture was unimportant at the time of Queen Elizabeth in spite of the fact that on the Continent, especially in the south where the climate was more propitious, it had been grown by the early Romans, even prior to the Roman invasion of England. The grain appears to have been imported into India where, in the early writings it was described as "food for the barbarians." It was introduced into the New World by the Spaniards, later by the French, Dutch and English settlers along the more northern seaboard.

The popularity of wheat over the other cereal grains lies in its excellence for bread making. Wheat flour is attractive in appearance, has a pleasantly mild flavor and may be leavened more satisfactorily than other types of flour. This is due to its large gliadin content.

There are over 300 varieties of wheat. The chief types are known as soft, semi-hard, hard and durum. The last is used in the preparation of macaroni. There are in general two types of flour, graham or whole wheat and patent or white flour. The former was named after Sylvester Graham (1794-1861), a physician who wrote extensively on dietetics. Entire wheat flour or whole wheat flour contains about one-half of the original bran. All of the bran is removed in patent flour. There are several grades of the latter.

Bread was first made either by the Egyptians or Chinese.

Wheat flour is used not only in the preparation of bread but in many other foods. It is usually present in pies, cakes, pastries, many cereals, macaroni, spaghetti, vermicelli, noodles. Cream sauces, gravies and soups are often thickened with it. Chicken is often dipped in flour and veal cutlets are often breaded. Postum contains some wheat, as do some varieties of sausage.

Wheat is often present in preparations the names of which do not suggest the fact. Rye bread as customarily made in the United States contains up to 50 per cent wheat flour. So-called rye flour, even if furnished by the mill, may contain some wheat unless pure rye flour is specified. Buckwheat flour, as usually purchased, contains some wheat, added because of its better keeping qualities. Pure buckwheat flour may be obtained. Boston brown bread contains rye flour, corn meal, graham flour and molasses.

There are a large number of proprietary breakfast cereals which are marketed under all sorts of trade names, many of which would not suggest the presence of wheat as a constituent. Tuft lists 63 prepared cereals and infants' foods which contain wheat. Of these, 39 convey by the name no suggestion of the presence of wheat. Some mention the other cereal flours but not wheat. Such are certain brands of buckwheat flour, corn flour, and corn and rice pancake flour.

Since the food allergic obviously should not eat substances the ingredients of which are unknown to him, it would seem logical to have available a not-too-long list of the prepared cereals with a description of all constituents. This listing will be discussed below.

Rye.—*Secale cereale*.—This grain is supposed to have originated in the Orient. It has been cultivated by man possibly as long as has wheat. Both were used in the bronze age as shown by their presence in the ruins of the Lake Dwellers of Switzerland. This grain grows in the same type of climate and soil as wheat, but will tolerate colder climates and poorer soil. It was not cultivated in ancient Egypt, India or Greece. Pliny, the Roman, described it as being grown at the foot of the Alps. Evidently, he did not relish it as a food since he adjudged "the grain detestable and good only to appease extreme hunger." It is the principal cereal of northern Russia, Scandinavia and northern Germany.

From it the German and Russian peasants make their black bread or pumpernickel. In the United States so-called rye bread almost invariably contains wheat flour also

So-called rye flour may contain wheat. One must specify "pure rye flour." Even the pumpernickel made in this country and sold at delicatessens may contain wheat.

Rye is grown principally in Russia, Germany, Austria and Hungary. In the United States, greatest production is in the Dakotas, Michigan, Minnesota and Wisconsin.

Rye is not as easily leavened as wheat, not containing sufficient gliadin. For this reason rye bread is likely to be heavy. The taste is stronger and is often masked with caraway seeds. An unleavened pure rye bread, really a wafer, is available in the Ralston Ry-Krisp which is especially convenient for allergies since it contains no wheat, egg or milk. The Scandinavian knackebrod is a whole-rye-meal hardtack. It is similar to Ry-Krisp.

With some patience, reasonably adequate leavened pure rye bread can be made. Horlamus bread (page 415) is an excellent example.

Rye has its principal use in the United States in the manufacture of whiskey.



Fig. 74.—Some cereal grains: long beard rye, oat, barley.

Some persons who are allergic to wheat also react to rye. Wells finds the alcohol-soluble proteins or prolamines of wheat and rye (gliadin) and of durum, einkorn, emmer, and spelt, all members of the wheat group, to be very closely related, apparently identical according to all immunologic tests applied. Hordein of barley is chemically similar to, but not identical with, the gliadin of wheat and rye, and immunologically is related to, but distinguishable from, gliadin. These prolamines are not similar to those of the corn group of cereals.

Barley.—*Hordeum distichon*.—This was probably the first grain crop of the human race, having been cultivated from remote antiquity. It was described in Egypt about 2440 B.C. where the Egyptians claimed it to be the first of the cereals used by man, introduced by their Goddess, Isis. It was a sacred grain to the early Greeks and was used in sacrifices and in the cereal festivals. Pliny designates it the most ancient cereal. The Chinese, the early progenitors of the Britons, made their bread from barley and the Romans the

chief food grain of England up until as recently as the middle of the eighteenth century. It is still widely used in northern Europe for bread making. It is not suitable for raised bread when used alone, on account of its lack of gliadin.

One rarely realizes the antiquity of barley in the manufacture of beer. The Cimbri of early England had it as their favorite beverage. The Egyptians used it as early as 540 B.C. It was a common drink among the Germans in A.D. 100.

Barley's greatest use is in the manufacture of malt. Pearl barley, the polished grain, is used as a breakfast food and as a pudding, especially by the Hebrews. It is also added in Scotch broth and other soups.

Just as rye is often used to give flavor to special breads, barley or malt is used as a constituent of breakfast cereals. Barley is present in the following cereals:

Brittle Bits	Maltine	Force
Grape Nuts	Falona	Malt-O-Meal

Malt is present in the following:

Corn flakes		John Bull Foods
Peter Pan bread	Post's Bran	Savoy and Moore's Food

Barley is often used in infant feeding.

One should realize that this is a desirable food product and is deleterious only to those who may be allergic to it.

Ratner and Gruehl demonstrated that persons who are allergic to barley may also react to barley malt and to malt extracts and brews. They found pure dextrimaltose sugars non-anaphylactogenic.

Malt.—This is barley—or other cereals, but most frequently barley—which has been allowed to germinate or sprout, with consequent production of diastatic enzymes. The great commercial value of diastase lies in its ability to readily convert starch into fermentable sugar. In the manufacture of alcoholic beverages the starch is first converted into sugar by the malt, after which the sugar is converted into alcohol by yeast. In the preparation of alcoholic beverages the malt is often added to other unmalted cereals such as corn, wheat and rice.

Beer, ale, stout and porter usually are made from barley, sometimes from wheat, rye, rice, oats and corn. Hops and yeast are also used. Barley or malt also enters into the manufacture of gin and whiskey. It is usually not used in the preparation of brandy, liquors, rum and wine.

Oats.—*Avena sativa*.—The native land of the common oat is uncertain, possibly Abyssinia, possibly the Danube Basin. It was not mentioned in the Bible and was therefore probably unknown in Egypt or Syria during Old Testament times. It appears in the Roman writings of Virgil and Pliny and of Dioscorides. The two latter state that the Germans used it as a porridge. Galen made similar statements but added that it is a fitter food for beasts than men except in times of famine. Oats were used by the Swiss Lake Dwellers in the Bronze Age. The Germans cultivated it two thousand years ago. The Hebrews, Egyptians, ancient Greeks and Romans did not grow it nor is it grown for human food in India today. It is grown especially in the northern part of Europe and in North America.

It is rich in protein and contains more fat than the other grains. Lacking much gliadin it cannot be leavened into bread. It is used rather in cakes. Its chief use is in cereals and gruels.

As is well known, rolled oats contain large quantities of roughage. Where roughage is to be avoided, as in individuals with colonic hyperirritability, the oatmeal gruel should be sieved.

Oats are used in the following breakfast foods, among others.

Salona	Maltine	Quaker Crackels
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They are also used in a number of prepared crackers and wafers, oatmeal cookies, etc., but fortunately their presence can easily be suspected by the presence of the husk.

Rice.—*Oryza sativa*.—This is the most extensively cultivated of the grains and is the principal cereal food for over one-third of the entire population of the earth. It appears to have originated in tropical Asia. It was introduced into China 3,000 years before Christ. The ancient Romans knew the grain but did not cultivate it, as we learn from the writings of Celsus, Pliny, Dioscorides and Galen. It was not introduced into cultivation in Europe until about 1522.

In the United States it is available chiefly as polished rice. Here it is cultivated in the Carolinas, Texas, Louisiana, Arkansas and California. It grows best under swampy or very moist conditions. Its climatic range is similar to that of cotton.

Orientalers do not customarily polish their rice. In this country the husk and outer layers of the grain are usually removed by polishing, with the resultant white rice that is commonly purchased. Coated rice is polished rice which has been coated with a thin mixture of corn syrup and talc which gives it a pearly luster.

Puffed rice is made by revolving the grain in sealed cylinders, heated to 550° F. The moisture within the grain is converted into steam and when the cylinder or "gun" is suddenly unsealed the steam within the grain expands with consequent puffing or explosion of the grain and pulverization of its starch granules.

Rice flour, ground rice, although not suitable for bread making for the same reason that applies to oats and rye, may be used for almost any other purpose for which wheat flour is appropriate such as the preparation of pastries and puddings.

Rice-macaroni is an Oriental product similar in appearance to solid spaghetti. It is a pure rice flour preparation.

The Japanese beverage, "saké," similar to beer, is made from rice.

Rice is available in prepared cereals as Puffed Rice, Rice Krispies and Rice Flakes.

It is a constituent of Dryco which is made from irradiated milk and contains a vitamin B extract of the rice polish. Rice is found in some of the prepared flours such as Aunt Jemima's Pancake Flour, Uncle Jerry's New England Corn and Rice Pancake Flour and so-called Rice Bread.

Ryzamine B, a concentrated vitamin extract, is derived from rice polishings.

Wild rice.—*Zizania aquatica*.—Known also as Indian rice, this is altogether different from, but related to, ordinary rice. It is indigenous to North America and eastern Asia. The Chinese Kaw-sun appears to be the same plant. Wild rice grows on the swampy borders of streams and in shallow water, and is found in such areas along Lake Champlain, the Hudson and Delaware Rivers, Canada, Lake Superior and the length of the Mississippi River. The plant is a tall grass, occasionally reaching a height of nine or even twelve feet. Difficulties of cultivation make it less readily available than common rice but it is a much more delectable dish. This was a very important article of food to the early Indians. It forms an excellent additional dish for those who must avoid wheat but may eat rice, especially so for those who object to the sticky gelatinous consistency of common rice. It is packaged in boxes of convenient size, is served without complete removal of the outer coating, and lends itself very well to serving with other foods such as hashes, seafoods, sauces, etc.

Corn.—*Zea mays*.—Maize or Indian corn appears to have been indigenous to the region of Mexico. It has been in cultivation since prehistoric times and is unknown in the wild state. Apparently it has developed from teosinte, a Mexican grass, or else both teosinte and corn had a common ancestor.

Columbus first saw corn in Cuba in 1492 and again in 1498 along the Venezuelan coast. He carried it to Spain whence it was rapidly distributed to most of the regions of the earth. When the New World was discovered corn was already being cultivated from Canada to Brazil and from California to Chili. Indeed, some of the Icelandic sagas describe what may well have been corn along the New England Coast as early as A.D. 1002.

The only cereal grains native to North America which were not imported by the white man were corn and wild rice.

Corn is eaten as such or mixed with other foods, such as the familiar succotash (Indian *Suquttahash*), a stew of green corn and green lima beans. Corn meal is used in many ways. Owing to its small gliadin content it does not make good loaf bread but otherwise is very good as bread. Much of the so-called corn bread, especially that prepared in the North, contains wheat flour. Pure corn bread has a crumbly consistency. Coarse ground white corn meal is usually called hominy. Corn pone (Indian *pone* or *apone*, or *oppone*, signifying bread) is a corn meal cake cooked in hot ashes. Ash cake is plain corn meal baked by the same process. Butter bread, egg bread or spoon bread, is made with white corn meal, buttermilk, butter, salt and eggs. Corn meal griddle cakes with maple syrup or honey make an excellent variant in the corn diet. Corn is a major constituent of the Irish "stirabout," the Italian polenta, and the Mexican tortilla and tamale.

Corn meal, the ground grain, is prepared in two ways. The old process or water-ground meal is made of whole corn that has not been kiln-dried and is milled between stones. It is excellent for corn bread but because of the fat content of the corn germ it does not keep well. New process or granulated corn meal is degermed, kiln-dried, and milled at a high

temperature between rollers. It keeps better than the water ground and blends more satisfactorily with other flours. There are a yellow corn meal and a white corn meal either of which may be prepared by both processes. White corn meal is preferred in the South while yellow corn meal is used more abundantly in the North.

Popcorn comprises several varieties of Indian corn with small ears and hard grains which contain a large proportion of endosperm. The process of popping is similar to that described above for puffed rice. Popcorn is grown chiefly in Iowa.

There are many uses for corn other than as a cereal grain. No other cereal is put to such a wide variety of uses. The sperm is divided into three parts, the germ (containing large quantities of oil) the endosperm (the body of the kernel, chiefly starch), and the hull or bran.

Corn oil is pressed from the germ at a high temperature. It is used as a cooking oil and for salads; Mazola oil is corn oil. It enters also into the manufacture of soaps and paints. Mixed with linseed oil it is marketed as a grinding oil. Corn oil is occasionally vulcanized into cheap rubber.

Corn oil may be used as a constituent of prepared salad dressings and is sometimes employed as a base for irradiated viosterol.

Cornstarch, from the endosperm is used in the kitchen as a thickening of gravies, sauces, soups, cream sauces, blanc-manges and puddings, and is used in large quantities in laundering. The writer has seen one patient allergic to corn who experienced urticaria each evening after retiring until after cornstarch was no longer used in laundering the bed linen.

Artificial or vegetable gum, known as dextrin and British gum, is made from the hydrolysis of the starch. These gums are used on postage stamps, envelopes and in many of the textile industries.

Corn syrup or commercial glucose or syrup glucose or so-called plain glucose is customarily manufactured from cornstarch. Karo corn syrup is an example. The same type of corn syrup is used in the manufacture of candies, jellies, preserved fruits, and imitation maple syrup to which mapleine is added. In candy manufacture, it is especially desirable for caramels because it does not readily crystallize.

The Indians of the time of Columbus made a fermented beverage from corn. The grain is still used in brewing and in the manufacture of corn whiskey.

Corn is present in a number of prepared flours and cereals. In many the word hominy or corn appears in the name. In others it does not. Examples of the latter are Cerealine Flakes, Mazuma, Nichol's Snow White S., Post Toasties, Quaker Crackels, Aunt Jemima's Buckwheat Flour, H. O. Company Buckwheat Pancake Flour, Purina Health Pancake Flour, Uncle Jerry's New England Self-Rising Buckwheat Flour, Pabulum.

Ratner and Gruehl concluded that corn syrups are nonanaphylactogenic. Although Ratner and Gruehl believe that crystalline sugars play no role in allergy, Urbach and Willheim have reported cases of idiosyncrasy to sugar and to salt.

TABLE XXVIII.—CHARACTERISTIC MICROSCOPIC DIFFERENCES BETWEEN THE COMMON COMMERCIAL STARCHES

(After Robbins, *Botany of Crop Plants*)*

All or most of the grains rounded, not from aggregates
Grains rounded, with central hilum; small grains globular or angular, <i>Wheat</i> .
Grains large, of various shapes, with excentric hilum, <i>Potato</i> .
Grains polygonal or rounded, with one or more facets, mostly from aggregates.
Grains very small, sharply angular, <i>Rice</i> .
Grains large, polygonal or rounded; hilum with clefts, <i>Maize</i> .

*P. Blakiston's Son & Co., Philadelphia, 1924.

Sorghum.—*Sorghum vulgare*.—This, like corn and sugar cane, is a member of the grass family. I know of no reports of allergy to it. Like millet, which is closely related to some of the hay fever producing grasses, especially barnyard grass, and panic grass, sorghum also has a close relative in the familiar Johnson grass. There are three varieties in general cultivation: the sugar sorghum from which so-called sorghum molasses is obtained; the grain sorghum; and the broom corn. Most of the food sorghum is used for stock, although the

molasses is eaten in the South. In the areas where the grain variety is grown, the ground seeds are sometimes used as a food, like corn meal and buckwheat flour, for the preparation of pancakes, mush and puddings or mixed with wheat flour in bread.

Sorghum appears to have been a native of Africa. It has been cultivated in China from remote times. The Chinese make bread of the flour. The best Chinese whiskey is distilled from the seed. It is now cultivated in tropical and subtropical countries on all of the continents except Australia. In the United States, Tennessee is the principal producer.

Cane sugar.—*Saccharum officinarum*.—We have seen that Columbus carried Indian corn to Europe on his first trip. On his second trip he made fair exchange by importing sugar cane into the West Indies, where today it is the chief crop. Originally a native of Bengal, the Indo-Chinese countries and the Islands of the Malay Archipelago, it was eventually carried into Africa by the Arabs and reached Europe during the eighth century. Today it is cultivated in every tropical and subtropical country.

Sugar was imported into Europe from the Orient before the Christian Era, along with spices and other costly products. It was used only as a medicine until the end of the Middle Ages, when it became customary to eat it as a sweetmeat. The common people did not indulge in this expensive luxury until the seventeenth century. Not until the nineteenth century did it become one of the main constituents of the diet. One hundred years ago the average annual per capita consumption in the United States was 9 pounds as contrasted with the present 94.

The name has been fairly well preserved from the original Sanskrit, *Sarkara*, with changes clearly traceable through the various languages as this commodity came into more general use in successive countries in its migration to England. *Sarkara* became the Prakrit *Sakkara*, then the Persian *Shakar*, the Arabic *Sukkar*, the Greek *Sakchar*, the Latin *Saccharum*, the French *Sucre*, and finally the Anglo-Saxon *Sugar*.

The possibility of allergy to the refined sugar is decidedly questionable. The writer has seen a few patients who have been quite convinced in their own minds that one or another kind of sugar has been responsible for allergic manifestations. The possibility exists, of course, that some other food article ingested with the sugar may have been the responsible excitant. Thus, in a series of 82 cases of migraine the writer found 8 patients who experienced headache following the eating of candy. They did not specify the type of candy but two were found allergic by skin test to chocolate, one to almond, one to cocoanut and one to peanut. The remaining three were not found allergic to any of the common ingredients of candies. The evidence, so far as it goes, suggests that in these cases it may have been one of the other ingredients than sugar which is responsible for symptoms.

Cane sugar allergy has been reported by Duke, and Rowe states that he has one patient who seems to be especially sensitized to it, although he was unwilling to state that this was definitely the cause.

In view of the prominence which carbohydrate substances are assuming as possible haptens, one cannot say categorically that refined sugar could not possibly be responsible for allergy. This is a problem for future solution. Since skin reactions are negative this procedure for establishing an etiologic significance is not available. The possibility exists that the leukopenic index might be of assistance in the study of this apparently rare problem.

On theoretical grounds one would anticipate a greater tendency toward sensitization to the less highly purified molasses. So far as I know no such cases have been reported. Molasses is the base for the manufacture of rum.

Cereal Grain Avoidance

In the preceding section we have discussed not only the cereal grains but those other members of the grass family, sorghum and sugar cane, which are more or less commonly used as food in the United States. There are other grasses, some portion of which is used as food, elsewhere in the world. Two notable examples are millet, used as an edible grain in parts of Asia; and bamboo, the tender shoots of which are considered quite a delicacy in China and Japan.

In mentioning the numerous avenues through which one may establish contact with refined products of the cereal grains, especially corn, I do not wish to imply that an individual allergic to the grains would experience symptoms following contact with any or all of these refined products. This certainly

has not been demonstrated and is indeed rather dubious. Ratner, for example, has presented evidence that persons allergic to corn will not experience symptoms from corn syrup and that persons allergic to barley do not react to dextrimaltose. At the same time it is obviously desirable that one should know the sources of all substances with which the allergic individual may be coming into contact.

Quite a number of persons have been found allergic to castor bean meal. I know of no reported cases of allergy to castor oil. On the other hand, cottonseed oil is said to retain its allergenic activity, and I have seen one patient who was allergic to olive oil. Stevens* finds that positive protein reaction does not always indicate that the subject cannot ingest purified cotton seed oil preparations.

The allergenic capacity of many of these refined products will ultimately be determined only after careful observation of the response to them on the part of the specifically and highly sensitized individuals.

The person who is sensitized to wheat or others of the cereal grains may be desensitized or, better, practice avoidance. Fortunately, one does not as a rule react to all of the grains, and one may, therefore, substitute those which fail to react. Even when one gives positive skin reactions to all, my experience has been that the leukopenic index may be negative to some of them. Subsequent experience usually indicates that the patient can partake of the leukopenic negative foods.

Withers found in a study of 27 persons allergic to one or more of the cereal grains that 10 were allergic to but one, 10 to two, 5 to three and 2 to four of them. Twenty-four gave positive reactions to wheat, 8 each to rye and rice, 7 to corn and 3 each to barley and oats. The 3 who had no symptoms from wheat did experience trouble from corn and rice. All who had trouble from rye, barley, and oats also had symptoms from wheat. These conclusions were not based upon skin reactions but on the actual experience of the patients following dietary trials over a sufficiently long period to be conclusive.

I have found positive skin reactions to wheat in 24 per cent of 200 food allergies, while none of the other cereals reacted positively in over 4.5 per cent. Rowe in a series of 175 patients found positive skin reactions to wheat in 30 per cent, with positive skin reactions to each of the other cereals in not over 4 per cent. These were the results of skin testing. As far as actual sensitization to these foods is concerned, as determined by the patient's subsequent response to eating them, he found 57 per cent sensitized to wheat, 5 per cent to oats, 3 per cent to rye, 4 per cent to rice and 2 per cent to corn. Vaughan found in a similar study of 82 cases of migraine that wheat was proved to cause symptoms in 23 per cent as against a little over 1 per cent for rye and barley, 2.4 per cent for rice, 3.6 per cent for oats, and 5 per cent for corn.

Eyermann found in a study of 95 cases of nasal allergy that wheat was responsible for symptoms in 31 per cent as contrasted with approximately 1 per cent each for oat and rye, 2 per cent for rice and 5 per cent for corn.

It is obvious from these several surveys that allergy to wheat is decidedly more common than to others of the cereal grains and that in a large number of cases one or more of the latter may be substituted for wheat. The present discussion, therefore, deals primarily with wheat avoidance and the employment of substitute flours.

*Stevens, Henry, Washington, D. C. Personal communication.

The patient who must avoid wheat is naturally desirous of knowing what sort of bread he may have as a substitute. There is no bread as palatable as wheat. After disappointments with one recipe after another the patient usually finds this out and often concludes that he would prefer to do without bread of any kind. Furthermore, nowadays, relatively little bread baking is done in the home and we have come to depend upon the bakery to supply these needs. In my experience the majority of allergic patients settle down to a pure rye cake such as Ry-Krisp or corn bread when these are allowed, fulfilling their starchy requirements with those prepared cereals which they are allowed and with the starchy vegetables.

Among the ready prepared native rye breads the writer can highly recommend the Ralston Ry-Krisp which is now available in a large proportion of the first class restaurants and on dining cars, and the Horlamus rye bread (see page 415) which is available in vacuum sealed tins, and therefore keeps for a considerable time.

For those who prefer to experiment in the kitchen, a number of wheat-, egg- and milk-free recipes have been formulated by those interested in allergy. Especially helpful is the *Allergy Cook Book* by Balyeat. An excellent series of recipes is also available in Rowe's volume *Clinical Allergy*. Experience has shown that the first effort is usually pretty much of a failure. Continued trial, however, usually results in a reasonably palatable product. The sponge cake and gold cake made with potato flour are really more delicious than are those made with wheat. Safe-Mix flour (soy bean and potato) may be used to make very acceptable breads and cakes.*

Buckwheat bread is very palatable, especially when cut thin and toasted lightly.

If one really wishes to prepare wheat substitute recipes, one will find quite an abundance of them in any good cook book.

Breakfast cereals.—The prepared cereals constitute a convenient substitute for the bread which is so universally a part of the breakfast. Thirty years ago, when the so-called breakfast foods were a novelty, the number of preparations was so great and the method of preparation so secret that any effort to use them in allergic dietary therapy would have been futile. Fortunately, however, the great majority have passed into oblivion and the present list, although rather long, comprises those which have established themselves either by merit, by tastiness, or by continued high pressure advertising. Today the manufacturer is not adverse to naming the ingredients, a fortunate fact for the allergic.

There are three general classes of breakfast cereals: (a) those which are crushed raw, (b) partly cooked, and (c) those which have been malted. In the latter group the starchy material has been partly changed into maltose and dextrin by mixing with malt. To a limited extent this is a process of pre-digestion. Corn Flakes are an example of this, the flakes having been dusted with malt.

Other Starchy Foods

Arrowroot.—*Maranta arundinacea*.—Starch may be obtained from other sources than the cereal grains. Arrowroot is a starch obtained from the root stock or rhizome of a West Indian plant which is also grown in the Gulf States, Mexico, and Brazil. It derives its name from the Indian custom of using the fresh root for the cure of poisoned arrow wounds.

*Made by the American Dietetics Company, Yonkers, N. Y.

Arrowroot starch may be used in the preparation of biscuits, puddings, jellies and cakes and may be added to milk, broths and bouillon, very much in the same way as cornstarch. The Bermuda arrowroot is reputed to be the best.

Sago. Coontie. Indian bread-root. Florida arrowroot.—*Zamia integrifolia*.—This starch is obtained from the trunk-pith and rootstock of a subtropical palm. The sago starch may be used in the same manner as arrowroot starch.

Cassava or manioc.—*Manihot utilissima*.—The cassava starch is likewise obtained from a tropical plant grown in the West Indies, South America, Java and the Malay Peninsula. Cassava flour or starch obtained from the root is also known as Brazilian arrowroot. It is used in the manufacture of yeast cakes. It is also used as a laundry starch, for sizing, for glazing twine, but chiefly in the preparation of tapioca.

Tapioca.—*Manihot utilissima*.—This is obtained from the cassava or manioc and is marketed in several forms as pearl tapioca, flake tapioca, granulated, and pulverized or tapioca flour. In cooking, the starch granules burst and the tapioca becomes a translucent jelly. It is especially appropriate for puddings and soups.

Sago.—*Metroxylon sagu*.—True sago is derived from the pith of the sago palm of the East Indies. This palm fruits once only, about the age of ten or fifteen years. Then it dies. Just before fruiting the trunk becomes gorged with starchy pith. It disappears during the fruiting process. The pith from which sago is derived is therefore removed from the trunk just prior to fruiting.

CHAPTER XXXVI

FOODS AND THEIR AVOIDANCE

MONOCOTYLEDONS (Continued)

The Palm Family.—*Palmaceae*

Coconut.—*Cocos nucifera*.—This palm was originally distributed through the islands and the countries bordering the Indian and the Pacific Oceans. Evidence strongly suggests that its original habitat was the western coast of South America. It was recognized in India as early as 1330. It was introduced into Florida by accident. In 1840 a vessel was wrecked near Key West and a large quantity of the nuts were thrown up on the beach.

When the nut is green there is a thin coating of white creamy substance in place of the firm white meat that develops later. The former may be eaten with a spoon and is said to be delicious. There is also a sweetish water. After ripening, these become the firm white coconut meat and the milk. Coconut is used in cakes and candies, frostings, etc. The oil, obtained from the meat, is used in cooking, nut-butter, oleomargarine, and the manufacture of soap. A patient, highly reactive to cottonseed preparations, tolerated Gold Dot Oleomargarine, said to be made from coconut oil.

The coconut milk consists essentially of a weak emulsion of coconut oil with a little gum and sucrose.

Date.—*Zizyphus lotus*.—The date palm has been grown in the Mediterranean region since earliest times. Fresh or dried it is a delicious fruit which, alone, will keep a man nourished for long periods of time. The date palms are male or female. Growing wild they are present in about equal proportions, but when cultivated one male tree serves for from 40 to 100 females. The fertilization of the blossoms of the latter is accomplished by dusting a sprig of the male flowers on each flowering branch of the female tree.

There are many varieties of dates, some measuring as long as three and a half inches, some being oval, others round, some sweet and others less so.

The date appears to have been the lotus of the little lotus eaters of Zerbi, the Island of the Lotophagi. On this Island the Roman Army on its way to Carthage was nourished several days on its fruit. It was described in Homer's *Odyssey*. Ulysses was able to persuade his companions to leave the fruit only by threats. This date-lotus was in no way connected with the lotus flower, the Egyptian water lily which, in history, was held in such high esteem and which today is in such favor in Japan and China. In the Orient this latter lotus also serves as a food. The black seeds, not unlike little acorns, are of delicate flavor. The hairy roots are pickled for winter use. The stems may be eaten. The root furnishes starch similar to arrowroot.

In the United States dates are marketed dried. Soft dates are said to be excellent fried in butter. They may be used in hot or frozen puddings. Patients on Rowe's Elimination Diet 4 or the preliminary straight milk diet of the escalator program can add much to the taste of their monotonous meal if dates are allowed. A combination of dates and cottage cheese is very agreeable. The dry date or camel date of Arabia is a general food article which may be ground into date flour and will keep in this form for years. In its native home the date leaf is cooked as "palm cabbage and the stones are ground into date coffee." There is also a date oil. As is true with most plants which contain sufficient carbohydrates, in its native land the sap of the date palm or the juice of the crushed fruit is fermented to produce the native palm wine or date wine.

In the Near East "date honey" is made by hanging bunches of fresh dates up to drain. The fruit is afterwards packed or pressed into cakes. For the Oriental trade fruits are packed in fresh date honey, in large jars. The date palm is grown as an ornamental tree in many of the more southern states and dates are being successfully cultivated in California.

Jujube.—*Zizyphus jujuba*.—This, the Chinese date, is related to the African date just described. Introduced into China from India and the Malay Peninsula more than twelve hundred years ago, this plant now yields an excellent desert fruit. When dried, it very much resembles the prune. It is reddish, brown or black. There is another variety which was introduced into Europe from Syria and is cultivated along the shores of the Mediterranean. It

has been naturalized in Italy since the time of the Emperor Augustus. It may well have had the same ancestor as the Chinese variety, since it is said to have been brought to Syria from India. The jujube was first introduced into the United States in South Carolina in 1837. It is now being successfully cultivated in California and Florida.

Today it has no relationship to the jujube of the candy store which usually consists of gum arabic or gelatin with any of a number of flavors. Originally the juice of the Chinese fig was an ingredient, but this is no longer true.

Pineapple.—*Ananas sativus*

This fruit is not closely related to any other food. Like corn, wild rice and coconut it is indigenous to the New World. The companions of Columbus first saw it at Guadeloupe Island in 1493. Pineapple decorations have been found in the stucco ornaments of Indian ruins in Yucatan. Sturtevant states that the fact it now rarely bears seeds implies that it has probably been cultivated in tropical America for many hundreds of years. Wild pineapple, containing seeds, has been found along the Orinoco and in Brazil and Guiana. Since its discovery it has been cultivated in China, India, Java, the Philippines, in several of the Pacific Islands, Africa and elsewhere. Its introduction into Hawaii was as recent as 1899.

Pineapple makes a very excellent substitute food for allergies since it is readily available, canned. Pineapple juice is a good substitute for orange juice. A finely flavored pineapple vinegar is also made.

Banana.—*Musa*

This, the most prolific food plant known, has never been successfully traced to its ultimate source. It has been indigenous from remotest records with practically every people of the torrid zone. The debate as to whether it existed in the New World prior to the arrival of the white man appears to be quite conclusively settled by facts such as that banana leaves have been found in prehistoric Peruvian tombs, that native Mexicans offered the "fat banana" as a sacrifice to one of their goddesses, and that on Columbus' fourth voyage in 1503 he found, at Costa Rica, that "the country produced bananas, plantains, pineapples, coconuts and other fruits." (Bananas were growing on the Sandwich Islands prior to their discovery by Captain Cooke in 1778.)

There appears to be almost an infinite number of varieties, as is the case with the apple. Other names applied have been plantain and Adam fig. According to Mohammedan tradition Adam and Eve used plantain leaves for girdles. The plantain and the banana are essentially the same plant. The usual differentiation is that the plantain is a large fruit which is customarily eaten cooked, while the banana may be eaten raw. The plantain may be a foot long and as large as a man's forearm.

In certain tropical areas banana or plantain serves as the chief staple food. The ancient Incas used it as such. Natives have learned to eat it raw, cooked, boiled, baked and dried, and have made a banana wine.

True seeds are found only in the wild varieties, the fruit of which is of decidedly inferior quality.

The banana plant has a superficial resemblance to the palm. This is because what appears to be the trunk actually is an overlapping of long vertical leaf stalks which grow up from an underground rootstock. The entire plant is cut down each time the bananas are harvested and a new shoot pushes up from the rootstock to take its place.

While there are many varieties of banana only a few reach the United States, some of the others being more delicious but difficult of transportation. Examples are the "fig," or "lady finger," which is very small and thin-skinned and the "cavendish" banana, grown in Barbados, which is richly flavored and of good size but is also thin-skinned and highly perishable. Choice between the red and the yellow varieties is merely a matter of taste.

A banana is ripe when the skin has taken on a rich yellow and has become speckled with brown spots. These are to be distinguished from the large dark blotches which result from bruises. For export, bananas are always picked green.

The food value of a banana about equals two slices of bread.

Banana provides variation for the allergic who is not sensitized to it. It may be eaten raw, sliced with other fruits, as a flavoring in ice cream, cake, etc., and may be pressed and fermented to make a mild alcoholic drink resembling cider.

The plantain here discussed is quite different from the buckshorn plantain or star-of-the-earth or the seaside plantain, members of the same family to which the English plantain and broadleaf plantain belong, and the leaves of which are occasionally used, especially in France, as a salad.

Ginger.—*Zinziber officinale*

This is the underground root, rootstock or rhizome of a reed-like plant which each year sprouts leafy stems three or four feet high. It may be likened roughly to the iris plant which each year sends up a fleshy leaf from the rootstock, the latter being the source of orris root. It grows freely in moist places in the tropics. The rhizomes are gathered after the stalks have withered. Ginger is obtained from the West Indies, especially Jamaica, India, Africa and Japan. There are two varieties, the difference being only in method of treatment. Coated or black ginger is from the older poorer root, from which the outer coating has not been removed. Uncoated or white ginger has had this coating scraped off. According to Ward, African ginger has an excellent strong flavor and is largely used in the manufacture of ginger ale and extracts. Borneo ginger is merely a trade name since no ginger is exported from Borneo. Japan ginger, or white ginger which has been bleached, has a fine appearance but is inferior in strength. Canton ginger is a preserve or conserve made from young green roots which have been boiled and cured in syrup and put up in cups or jars. This is made both in China and the West Indies. Crystallized ginger is made from young roots. Leaf ginger is the root shaved into thin flakes.

Ginger is employed in the manufacture of ginger ale, ginger beer which is more popular in England than in America, Jamaica ginger, an alcoholic extract of the root, and ginger tea, an old-fashioned cold remedy.

Ginger ale, according to Ward, is a blend of ginger, red pepper (capsicum), lemon and other flavors such as sarsaparilla, with caramel for coloring, incorporated into distilled water and carbonated.

The Lily Group.—*Liliaceae*

This group of foods like that previously discussed is monocotyledonous. The chief food plants are onion, garlic, asparagus, chives, leek, shallot and Welsh onion. The outstanding ornamental plants of this family are the lily, tulip, hyacinth, and yucca. Most of the members of this family are fleshy herbs which develop from bulbs, although aloe sometimes develops as a shrub or small tree. Most of the foods in this group bear bulbs. Asparagus, leek and the Welsh onion are exceptions. The bulbs of chives are very small.

It is a point of some interest that in Bermuda the two plants best known by Americans are the onion and the lily, two closely related members of the same family.

Onion.—*Allium cepa*.—This has been a food for man since earliest history. The Children of Israel complained to Moses of its absence in the Wilderness. In Egypt it was a commonly used vegetable, fed to the slaves who built the great pyramid. Indeed, according to eastern tradition, when Satan walked from the Garden of Eden after the fall of man, onions sprang up at the spot where he placed his right foot, garlic from his left. The origin of the plant is unknown, but it is presumed to have been the Far East.

Socrates mentioned onion as a commonly eaten food. The Romans knew it well. It was grown in British gardens as far back as records carry us. Chaucer (1340) mentioned onion, garlic, and leek. From the writings of Albertus Magnus in the thirteenth century, it would appear that at that time the leek and garlic were favored over the onion.

It cannot be determined definitely from the records whether the onion family existed in America prior to the time of Columbus. Onions were growing abundantly in Mexico seven years after its discovery by the white man.

The members of this group of foods contain large quantities of a sulphur compound, allyl sulphide, to which are due the odor and taste. The edible portion of the plant is the fleshy base of the leaves. Onion is used not only as a vegetable but also as a flavoring and care must be taken in its avoidance if one is allergic thereto.

Garlic.—*Allium sativum*.—Well known to the ancients, this food appears to have originated in Tartary. Like onion it was badly missed in the Wilderness. The Romans disliked it but fed it to their laborers for strength and to their soldiers for courage. Cortez fed on it in Mexico. Onions and garlic were fed to the laborers who built the pyramids, to give them strength.

In the United States garlic is used chiefly as a flavor and may be found in soups, sauces, salads, pickles and sausages. At certain seasons garlic and the wild onion are abundant in the pastures and may produce an unpleasant odor and taste in milk and butter from cows which have fed upon them.

Leek.—*Allium porrum*.—Cultivated since earliest times, leek is said to be native of Switzerland. Nero was especially fond of leeks, eating them several days each month to clear his voice. In the sixth century the Welsh attributed their victory over the Saxons to the fact that they wore a leek as a badge to distinguish them from their enemies during battle.

The leek is used much in cookery, more in France than in the United States. The lower or blanched portion is best and may be eaten in the same way as asparagus and onion. The leaves are used to season soups, salads and stews. With the leek as with all members of this family, cooking partially destroys the rank odor and taste.

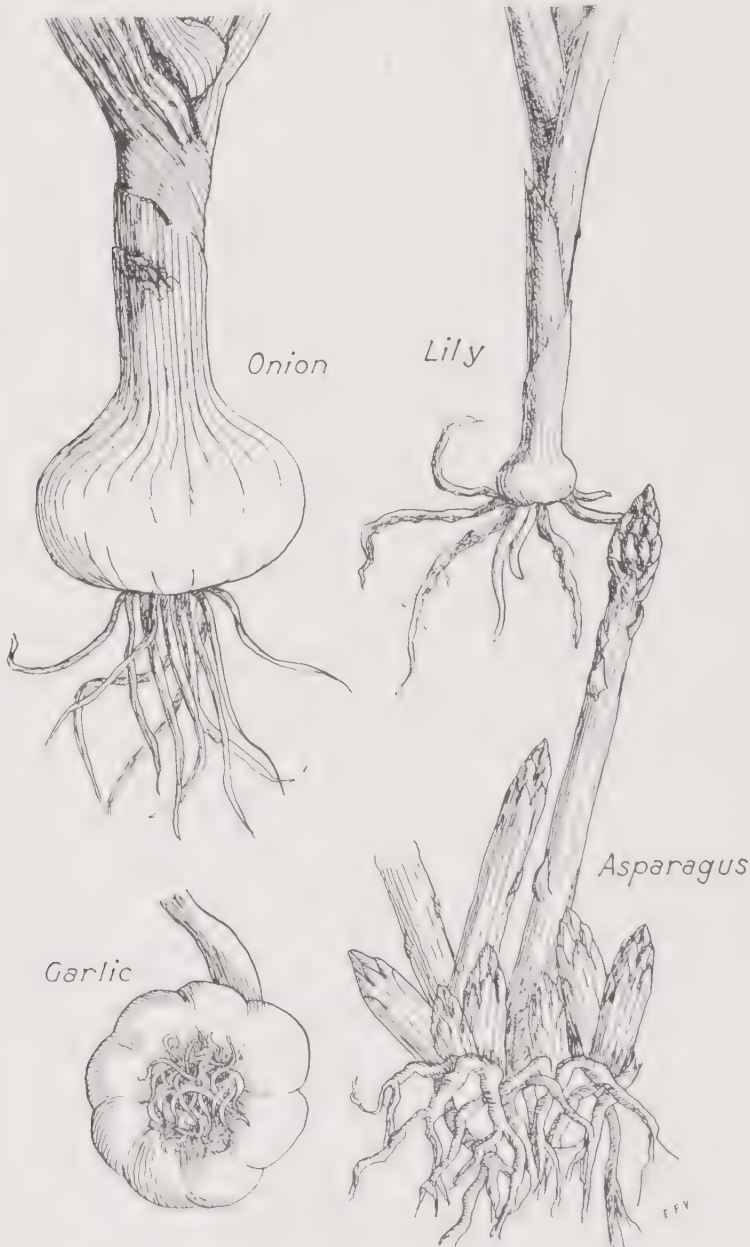


Fig. 75.—The lily family. General resemblance of secondary vegetative characteristics is obvious.

Chive.—*Allium schoenoprasum*.—This is grown principally for its leaf which may be used in stews, soups, and salads and especially in omelets. It is more popular in Scotland than elsewhere.

Shallot.—*Allium ascalonicum*.—This plant is said to have found its origin in Syria and to have been distributed through Europe by the armies returning from the Crusades. It is much more widely grown than chive, being fairly abundant in the United States. The

small red onion is often sold as shallot. In cookery it is used as a seasoning in stews and soups. Cut into small sections it sometimes appears as an ingredient of salads or sprinkled over steaks and chops.

Asparagus.—*Asparagus officinalis*.—Although a member of the lily family, asparagus belongs to a different genus than those foods which we have been discussing. It may well have taken its origin from the Caucasian regions in Siberia but at any rate was found growing wild in the Mediterranean area in the days of the Greeks and the Romans. It was being cultivated in Rome about 200 B.C. Nero was partial to leek while the Emperor Augustus loved his asparagus.

The edible portion of the asparagus is the tender shoot, which is cut shortly after its emergence from the ground. White asparagus is the same as the green except that it is kept beneath the earth for a longer time during its upward growth by banking up of the dirt around it. Although only the shoots or spears are eaten in this country, in Europe the seeds are used at times for a coffee substitute and a fermented beverage has been made from the bulb. The soft pulp of the plant may be separated from the fiber and is canned in the form of a thick paste which may be used by those whose dietary restriction does not prohibit asparagus.



Fig. 76.—Garlic (left), leek (right).

The common garden variety is the only species of asparagus which is edible. There are several others which are used for ornamental purposes, the commonest of which are smilax and the asparagus fern.

Yucca or Spanish bayonet, a southern plant, growing especially in the arid Southwest, has fruit which ripens in a cluster at the top of the plant. The fruit has a thick, tender rind and a seedy pulp. It may be cooked, according to Ward, in any way suitable for apples.

The Mulberry Family.—*Moraceae*

This family contains a surprising number of old "friends," some of which serve as foods. The fig, mulberry, and the breadfruit of the tropics are examples of the latter. The India rubber plant of greenhouses, osage orange, hop and hemp are other members. Some of these are trees, some shrubs, and some are merely herbs with a milky sap.

Mulberry.—*Morus*.—This is a fruit which could well be used to advantage by those allergies whose sensitizations have deprived them of a wide variety of fruits. The mulberry tree of Japan is actually a tree which may reach a height of sixty feet. *Morus nigra* is

varieties, the white mulberry used in the silkworm industry, native of China and Japan, whose berries are not particularly good; the black mulberry, native of Persia and Caucasus, used in Europe for the feeding of silkworms until the sixteenth century when it was superseded by the white mulberry, and whose fruit is quite edible; and the red mulberry, native of North America, the fruit of which is very tasty when eaten raw and excellent for cooking, especially when mixed with a more acid fruit such as apple and rhubarb and cooked in pies and puddings. There is a dried mulberry. The berry resembles very much the raspberry in general appearance but while the latter is a single fruit borne on a receptacle from which it is easily removed, the mulberry is a cluster of minute fruits along a single spike.

Hop.—*Humulus lupulus*.—Hop is added to beer chiefly to give it a slightly bitter taste and because of its alleged bacteriostatic activity. It has been used for this purpose from ancient times and was well known to the Romans, being mentioned by Pliny. Even in his time the buds or first sprouts were eaten as salads, since he described them as “more toothsome than nourishing.”

Fig.—*Ficus carica*.—This plant is a native of the eastern Mediterranean section. It has been cultivated from time immemorial. According to Grecian legend Demeter brought the first fig trees to Greece. Another legend has it that the tree grew up from the thunderbolt of Jupiter. The plant was introduced into England about 1525. Cortez carried it to Mexico in 1560. It was being cultivated in Virginia in 1669. The Franciscan Mission Fathers introduced the black fig into California where it is widely grown today. The fig is now cultivated through most of the states of the South. In Florida there are two native figs, not importations, which are, however, inedible.

The fig is a plant of unusual interest in that a particular insect is necessary for fertilization. The fig wasp, about one-eighth inch long, develops only in the wild fig or caprifig, the probable ancestor of all cultivated figs. We usually speak of the fig as a fruit. Botanically, however, it is a fruit receptacle, a fleshy organ which holds the true fruit or seed. At the end of the fruit receptacle is a small opening, the “eye,” or orifice. It is ringed by miniature leaves and the flowers grow inside the receptacle. The fig wasp enters the eye to deposit its eggs in the ovaries of the fruit. In doing so it inadvertently also deposits pollen. The finest edible variety, the Smyrna fig, has only pistillate flowers. There are no stamens. No pollen is manufactured. However, for the best fruit the Smyrna fig must be pollinated. It is only after this process that the fruit develops the delicious aromatic nutty flavor that makes it superior to other varieties.

The fig culturist provides for fertilization in the following manner. The larval wasps grow in the caprifig. When fully developed they emerge from the eye, covered with pollen. Their task is to seek out other caprifigs in which they may deposit their eggs. The fig culturist, just prior to their emergence, hangs the caprifig, containing the fig wasps in the Smyrna fig tree. This is accomplished by placing a number of figs in wire baskets which are then hung upon the branches. The wasp, leaving the caprifig, immediately enters the orifices of the Smyrna fig, seeking the proper place to deposit its eggs. However, the styles of the pistillate flowers of the Smyrna fig are so long that the wasps are unable to lay their eggs in the proper place. They perish in the fruit and their bodies are absorbed by the growing cells. But they have transferred the pollen.

Some figs do not require caprification or fertilization, while others do. Each tree produces two or three crops each year, the earliest being from the old wood of the tree, the later ones from the newer growth. In some varieties caprification, fertilization with the pollen of the wild or caprifig by means of the fig wasp, is necessary only with the first crop; in others only with the later crop; some figs like the Smyrna will not mature at all unless their blossoms are pollinated. At the other extreme, there are varieties which do not require pollination at any time.

With different varieties the first crop may contain only staminate flowers, the second only pistillate or vice versa. The need for caprification or otherwise in the different successive crops obviously depends upon whether the staminate or pollen-producing elements are present. The Smyrna fig never has other than pistillate flowers. In the figs which have not been fertilized the fruits or “seeds” are merely empty little shucks.

The fig orchardist must, therefore, have three elements for successful production of his fruit: the cultivated fig tree, the wild fig or caprifig, and the fig wasp which develops only in the latter and which inadvertently carries the pollen from the caprifig to the other varieties.

The common fig is a shrub or small tree rarely more than 25 feet in height. Some varieties are woody climbers. The golden fig commences as an epiphyte, the seed germinating in the crevices of other trees, after which aerial roots grow out, until they strike the soil. This being accomplished the root eventually becomes trunklike. The banyan seed, another

variety, does likewise. When once rooted in the soil it stands independently of its original host tree. Many aerial roots may be put down which later grow to large size. As a consequence, in the East Indies the banyan is "known as an immense living columned hall, consisting of a plant with an expanded canopy of leaves and numerous stem-like crop roots growing down from the boughs."

Figs may be eaten fresh or dried. Medicinally, they are used in syrup form. With no pharmaceutical houses in ancient times, no pills or tablets, one can understand the plant having been held in high esteem as a pleasant natural laxative.

Breadfruit.—*Artocarpus communis*.—According to Sturtevant the breadfruit tree affords one of the most generous sources of nutrition that the world possesses. Twenty-seven trees which would cover an acre with their shade are sufficient for the support of from ten to twelve people during the eight months of fruit bearing. It is native of the tropical islands of the South Pacific. First described in 1695, it has since been naturalized in tropical America and Jamaica. The fruit is about the size of a child's head, with reticulated surface, a thin skin and a core about the size of a small knife handle. The edible portion lies between the skin and core, is white as snow and of the constituency of new bread. It is rather sweetly insipid in taste and is best eaten baked or roasted, when it has the constituency of a custard pudding and somewhat the taste of sweet potato.

Nowhere does it grow wild. It appears to have been an ancient product of cultivation by the natives of the Pacific Islands. Sturtevant states, "in the cultivated breadfruit, the seeds are almost always abortive, leaving their places empty, which shows that its cultivation goes back to a remote antiquity."

Breadfruit is preserved by the natives who bury it in deep pits where it ferments and becomes of the constituency of cheese. It then has a very unpleasant odor and taste which is greatly relished by the natives.

The Buckwheat Family.—*Polygonaceae*

The two edible members of this family are rhubarb and buckwheat, familiar to all and characterized especially by their large heart-shaped leaves. Under exceptional circumstances the rhubarb leaf may measure a yard across.

Among the other members of this family we are especially interested in rumex or dock since its pollen is responsible for some pollinosis.

Rhubarb.—*Rheum raphaniticum*.—Rhubarb, or pie plant, originated in Asia. The several varieties have come from China, Tartary, the Himalayas, Mongolia, southern Siberia and the region of the Volga. It was introduced into Europe in 1608 where it was first cultivated at Padua, Italy. While it was grown in England in about 1773 it was not used as a culinary plant until about 1827. It was introduced into the United States about 1800, being used for tarts and pies.

It still serves this purpose excellently, providing a rather acid, tart taste, not unlike that of apple. It is somewhat laxative and extracts of it are used medicinally for this purpose. The leaf should never be eaten since its oxalic acid content is high.

Buckwheat.—*Fagopyrum vulgare*.—Common buckwheat has been cultivated in China for over 1,000 years. According to one authority, it was introduced into Europe from northern Asia at the beginning of the sixteenth century. According to another, it was brought back by the armies returning from the Crusades. It was introduced into America in New Amsterdam in 1626. It is now common through the northern states and Canada, being most abundantly grown in New York and Pennsylvania.

The edible portion is a large grain somewhat resembling a beechnut. This explains the derivation of the name, taken from the German *buchweizen*, meaning beech-wheat. The flour is used chiefly for batter cakes. Alone, it is dark and rather bitter and is therefore customarily mixed with some other flour such as wheat. This improves the taste and cooking quality. An allergic may also be exposed to buckwheat in honey. Buckwheat honey is regarded by many as especially delicious.

Much of the so-called buckwheat flour is not pure but mixed with other flours. Pure buckwheat flour may be obtained, usually directly from some small neighborhood mill. It should be purchased in small quantities since insects are readily attracted to it and its keeping qualities are not good.

Jewish Kasha is said to be a pure buckwheat soup. It may be obtained from delicatessen stores.

CHAPTER XXXVII

FOODS AND THEIR AVOIDANCE—CONTINUED

DICOTYLEDONOUS FOODS

Walnut Family.—*Juglandaceae*

Walnut.—*Juglans baccata*.—The so-called English walnut is a native of the territory between Greece and the Himalaya Mountains. In the United States this was termed English because in the early days it was imported from England. Today fifty per cent of the English walnuts consumed are grown within the United States and of those imported one-third come from France. Black walnuts and white walnuts or butternuts are native of North America. Both of the latter are dark shelled. The term black refers to the dark brown bark of the tree, while the term white as applied to butternut refers to the light grey bark. Butternut is quite oily. The Indians used this oil for seasoning their food.

There is a walnut oil made especially in Germany and Switzerland, of a delicate nutty flavor which is obtainable in the United States and may be used in place of olive oil.

Pecan.—*Carya olivaeformis*.—This is indigenous to the southeastern United States, the Mississippi Valley and the river valleys of Texas. The name is derived from the Indian term *pecaund*. The Indians of Louisiana expressed the oil which they used as a seasoning for their food. Pecan is a variety of hickory.

Hickory.—*Carya alba*.—This tree grows only in North America.

Beech Family.—*Fagaceae*

Chestnut.—*Castanea*.—The European chestnut is said to have been indigenous either to the south of Europe, from Spain to the Caucasus, or to Asia. It was abundant in Italy at the time of Virgil. The peasantry of certain sections of South Europe even today rely upon the chestnut as a main food. Such places are the Apennine Mountains of Italy, Savoy in the south of France, Sicily, Tuscany, and parts of Spain. In these territories the nut is ground into a flour from which bread and puddings are made.

The American chestnut appears to be indigenous to America, growing along the Atlantic Seaboard and as far west as Michigan. The chinquapin is a small but very pleasant-tasting chestnut, growing in the southern United States.

Chestnuts favor especially mountainous districts, areas where cereals cannot be satisfactorily raised. This accounts in part at least for their popularity as a basic food in the mountainous districts of southern Europe. The chestnut blight of a few years ago in the United States destroyed the majority of our chestnut trees.

Chestnut flour is available. The marron, a large chestnut grown in France and Italy, is delicious when fresh roasted. In this country it is available in preserved form or coated with sugar ice (*marron glacé*).

The horse chestnut is inedible, chiefly due to the bitterness of the seed, although it has been used as a substitute for coffee. It is a native of Greece and the Balkans and was imported into America. The California horse chestnut, a low spreading tree of the Pacific Coast, has also a bitter nut which, however, was formerly used by the western Indians in soups and gruels.

Filbert. Hazelnut. Cobnut.—*Corylus*.—The North American variety, called hazelnut, is smaller than, but as tasty as, the European variety, filbert and cobnut. The latter took its origin in Europe and Asia Minor. It was cultivated by the Romans and derives its name from Philibert, a king of France who “caused by arte sundry kinds to be brought forth.” The best varieties, Barcelona nuts, come from Spain. Many are grown in Kent, England. They were first imported into America in 1629. In Kazan, Russia, where the nuts are extremely plentiful, an oil is expressed for use as a food.

Wintergreen.—*Gaultheria procumbens*.—Although the true wintergreen is a member of the heath family, wintergreen flavoring or extract is usually obtained from the birch, sweet or black, the twigs and leaves of which yield a chemically identical oil.

Beechnut.—*Fagus ferruginea*.—The nuts are small, triangular, and grow in pairs, covered with a prickly burr as is the case with most nuts. There are American and European varieties. Although small the meat is most palatable. The roasted nuts in France serves as a coffee substitute. In Germany the nut oil is used as a salad oil and as a butter substitute.

The Oak.—*Quercus*

Acorn.—*Quercus esculus*.—Acorns are not customarily eaten in this country, but “sweet acorns” are still quite popular in southern Europe.

The Beet or Goosefoot Family.—*Beta*

Although the principal cultivated members of this family are beet and spinach, a number of weeds which are of importance in allergy, especially in causing pollinosis, are also members. Chief among these are Russian thistle, lamb's quarters, pigweed and goosefoot.

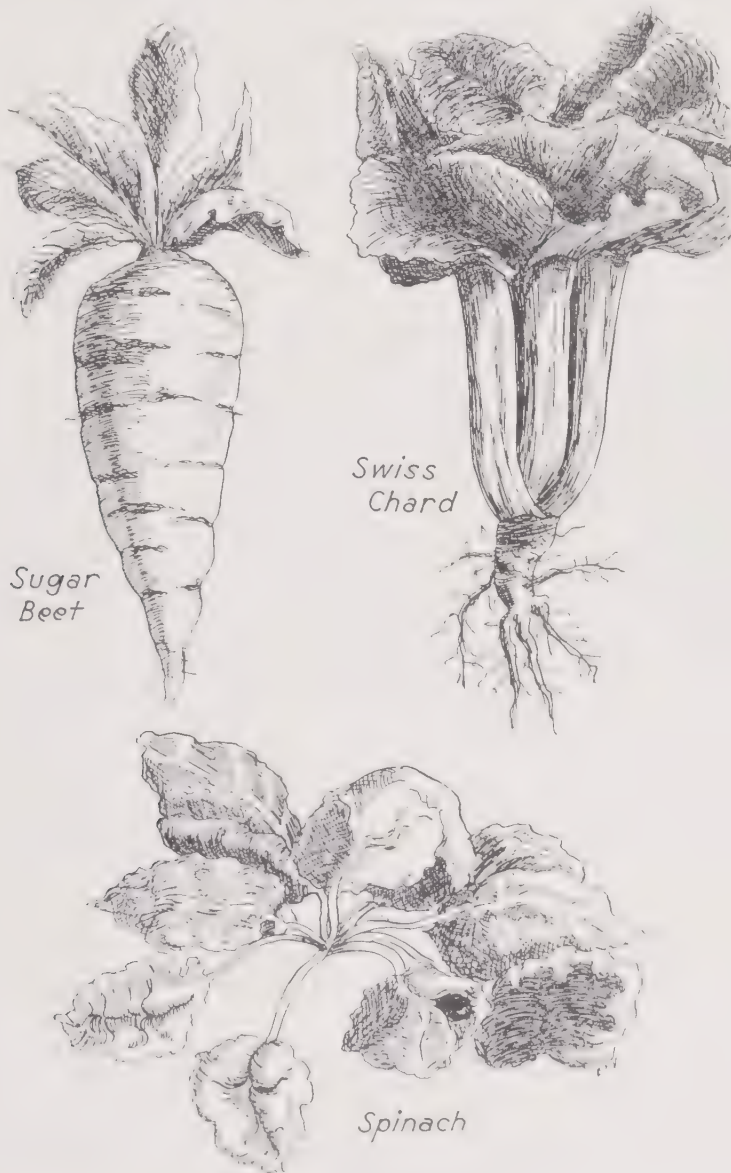


Fig. 77.—The beet family.

Chard. Swiss chard. Sea kale.—*Beta cycla*.—This was a predecessor of the better known beet. The chard has a well-developed edible leaf which is used as a salad, or the leaf and stem may be prepared and eaten like asparagus. The root is insignificant. The beet has been developed from the chard by the breeding of a large fleshy root plant. Its original home appears to have been North Africa. Chard was mentioned by Aristotle and by the Greeks and Romans who followed him. Galen and Dioscorides mentioned it, but only as a medicine.

The term chard is also sometimes applied to the stalks of artichoke, cardoon, and some other plants.

Beet.—*Beta vulgaris*.—This is relatively a modern vegetable. It first came into use in Germany and England in the sixteenth century. It was introduced into the United States from Europe.

The sugar beet is but a variety of the common beet, selected on account of its high sugar content. The sugar beet industry was started in France in 1811. Fifteen years later 1,500 tons of sugar were being produced annually from the sugar beet. Today half of the total sugar output of the world is from beets.

Wind is the chief factor in dissemination of beet pollen.

Spinach.—*Spinacia oleracea*. While a member of the same group, spinach is not as closely related to Swiss chard and beet as they are to each other. It appears to have been introduced into Europe through Spain. Like beet, it is relatively a newcomer, having been first described as an edible in 1351. In 1390 it was mentioned as one of the vegetables for use in the Court of King Richard the Second.

New Zealand spinach, mountain spinach and orache are not true spinaches. They may be eaten even though one is allergic to true spinach.



Fig. 78.—Comparison of beet leaves (left) and spinach leaves (right).

The Gooseberry Family.—*Grossulariaceae*

The two edible members of this family are the currant and the gooseberry. Both have originated in cooler climates rather than warmer, as most of the foods which we have previously discussed have done.

Currant.—*Ribes rubrum*.—The currant is said to have reached culture from the Danes or the Normans. Improvements in the varieties were made in The Netherlands. These improvements appear to have been obtained by planting seedlings of unusually good wild plants in gardens where the soil and other facilities for development were optimal. The currant was not described prior to the sixteenth century. However, very early after its first mention it was described as a border plant in gardens, recommended both for its foliage and its fruit.

The red currant was brought to this country from Europe. The Buffalo currant, also called the Missouri currant or golden currant, was native to the Missouri and Columbia Rivers and was first brought to the East by Lewis and Clark on their return from their famous expedition. The Buffalo currant is cultivated in Utah for its fruit. There is a black currant of North America and another of Europe and Asia. All currants are berries primarily of northern countries extending southward principally along mountain ranges.

The currant is a small acid berry usually used in jelly, jams, preserves, and pies.

Dried currants, as used in cakes, biscuits and the like are not actually currants. They are small seedless raisins grown principally on the Grecian Islands of Zante. One who is allergic to grape should, therefore, avoid dried currants.

Gooseberry.—*Ribes grossularia*.—This is a very similar plant which developed in Europe, North Africa and the Himalayan region. Its original habitat was northern Europe. It was unknown in the Mediterranean area in Greek and Roman times. It was first mentioned in the sixteenth century at about the same time as the currant. There is also a native North American wild gooseberry first described in New England in 1609.

This berry has been most perfected in England where it is consumed in large quantities. It is not as popular in this country since our native varieties are not as good. Good gooseberries in England often reach a full inch in diameter.

Gooseberries are used for the same purpose as currants. They are especially good in pies, cooked either green or ripe, and because of their tartness they add to the taste of a sauce. Up to the present, attempts to cultivate English gooseberries in this country have not been successful, chiefly due to their susceptibility to gooseberry mildew.

Kennedy (1936) has reported atopic eczema from gooseberries.

The Cabbage or Mustard Family.—*Brassicaceae*

This family comprises a large group of vegetables: cabbage, turnip, broccoli, Brussels sprouts, cauliflower, collard, kale, kohlrabi, rutabaga, savoy cabbage, charlock and the mustards. They are all very closely related and probably all came from a common ancestor. For this reason, and with crossed allergic reactions common in this group, if one has observed one or more positive reactions to individual members, it is safest to recommend avoidance of the entire group. One may almost say that mustard is the seed, kale and cabbage the leaf, Brussels sprouts a diminutive head, broccoli and cauliflower abortive flowers, kohlrabi an enlarged fleshy stem, and turnip and rutabaga an enlarged tap root of what is practically one and the same plant, the differentiation depending on what portion of the plant has become overdeveloped.

The entire group appears to have been first grown in Europe and northern Asia, especially in the cooler climates such as Russia, Siberia and the Scandinavian Peninsula. Even today they do best where it is not too hot. Now they are cultivated practically throughout the civilized world.

Turnip and rutabaga.—*Brassica campestris*.—These appear to have been primarily of northern origin, from the region between the Baltic Sea and the Caucasus. The rutabaga or Swedish turnip was developed on the Scandinavian Peninsula. It was known in France as early as A.D. 42. The Romans spoke of it. Rutabaga was introduced into England in 1790.

Cabbage and kale.—*Brassica oleracea*.—The kale is essentially an open leaf cabbage. It had many other names in former times such as cole, borecole and colewort. This explains the derivation of the familiar term cole slaw, cole being an old term for kale and slaw a Danish term for salad. The kale is an open plant, not heading up like cabbage nor producing edible flowers like cauliflower and broccoli. There are many varieties depending upon the appearance of the leaves which in many cases closely resemble each other. Kale was very popular among the Greeks and Romans.

Like kale, cabbage presents many forms. That the ancient Greeks held this plant in high esteem is indicated by their fable that it sprang from the perspiration of the brow of Jupiter. The Egyptians worshiped the plant and Greeks and Romans alike recommended it as a preventive of drunkenness. However, research indicates that the cabbage of the Greeks and Romans was not the present-day head cabbage but a loose-headed variety more resembling kale.

Cole slaw and sauerkraut are special preparations of cabbage. The former is usually made with French dressing which contains vinegar and the latter always contains yeast. It is a fermented cabbage.

Collards, *Brassica oleracea acephala*, is a variety of kale whose leaves are produced in tufts or rosettes and which are cut and used as a spinach. The term collards is also applied to young cut leaves of any cabbage. True collards withstand heat and are grown especially abundantly in the southern states. However, they develop a much better taste after frost.

Cauliflower Broccoli.—*Brassica oleracea var. botrytis*.—If a member of this general family develops chiefly leaves, which show no tendency to turn inward, it becomes an open cabbage or kale. If, however, the growth is stunted, the joints are short and leaves turn inward, this becomes a head or heart cabbage. If, instead of either of these tendencies, there is an unusual tendency to the formation of flowers, the result is a cauliflower or broccoli. There

is some evidence that broccoli was known to the Romans. It was not introduced into England until 1720. Broccoli was the original form of the cauliflower, the chief difference being that in the former the heads are smaller.

Brussels sprouts.—*Brassica oleracea* var. *gemmifera*. This has been grown in the region of Brussels, Belgium, at least since the thirteenth century. It is in essence a cabbage which has grown a large stem, along the side of which axillary leaf buds develop into small heads of cabbage or sprouts. Each bud grows a miniature cabbage.

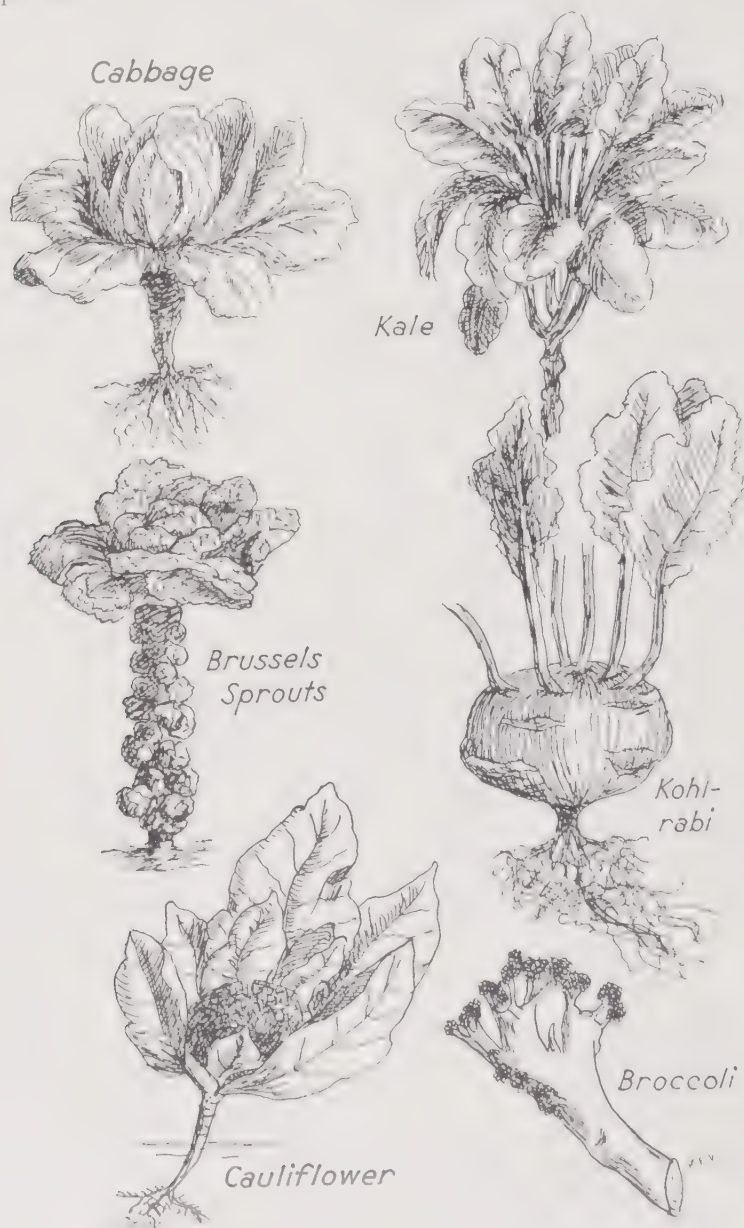


Fig. 79.—The cabbage family.

Kohlrabi.—*Brassica oleracea* var. *caulo-rapa*.—It is interesting to observe how the term *cole*, former name for kale, persists with alterations in the development of the various species which we have been discussing. We see it in *broe-coli* and in *cauliflower* which was formerly *colli-flower*, in *collards* or *cole-wort* and here again in *kohlrabi*. This last appears to have been one of the latest additions to the cabbage group, not having been described definitely prior to 1564. According to some writers it is a cross between the cabbage and rape (a variety of turnip chiefly grown as stock feed). The derivation of the name from *cole-rape* appears traceable. Although *kohl-rabi* appears very much like the turnip, the difference is that while the latter is a tap root and grows beneath the ground, the former



Fig. 80.—The cabbage family showing resemblance of vegetative characters (leaves). Top row: radish, collard. Middle row: Brussels sprouts, cabbage. Bottom row: broccoli, kale.

is a fleshy stem growing above ground developing from the stem, just above the cotyledons. Leaves sometimes grow out of the upper part of this fleshy stem as well as from the stem above.

Mustard.—*Brassica nigra*.—Black (or brown) mustard was a plant of the ancients, supposedly made known to mankind by Aesculapius, the God of medicine, and Ceres, the Goddess of the seeds or harvest. It was used by Hippocrates 480 B.C. It is cultivated widely, but especially in Alsace, Bohemia, Italy, Holland, and England. It has escaped from cultivation in Europe and in the United States and is at times a troublesome weed. Charlock, another variety of the same family, is one of the worst weed pests in the grain fields of the Middle West.

The use of mustard as a condiment dates from 1720 when an old woman living in Durham, England, developed a method of grinding the seed in a mill and separating it from the husk. She kept this as a secret process for many years. Present brands of prepared mustard are still termed "Durham Mustard." The pungency of table mustard does not exist in the seed itself and only develops after the ground seed has been mixed with water, when a specific enzyme produces the volatile oil, from a glucoside of the seed. Most table mustard contains, in addition to the ground mustard, flour, vinegar, and water. Sometimes other condiments are added. Pure mustard flour may be obtained.

Mustard greens and mustard salad are usually made from the leaves of white mustard, which is milder than the black.

Radish.—*Raphanus sativus*.—This plant probably had a different remote ancestor from the members of the cabbage family previously discussed. However, it is quite closely related. It takes its origin from China. Radishes were cultivated in Egypt in the time of the Pharaohs. The Greeks esteemed it so highly that in presenting their gifts to the God Apollo, the representations of turnip were made of lead, beets in silver but radishes in beaten gold. It was used medicinally to such a extent that an ancient Greek physician wrote a book on the radish. It was introduced into England in 1548 where it was "used as a sauce with meats to procure appetite." The radish is still a relish, since it has practically no nutritive value.

Horse-radish.—*Radicula armoracia*.—This and water cress belong to yet another group of the cabbage family. Another name for horse-radish is red cole. It is indigenous to eastern Europe from the Caspian to Finland. Grown for the white flesh of its very pungent root, it is customarily grated and dispensed in jars.

Water cress.—*Radicula nasturtium-aquaticum*.—The young shoots and leaves of this plant have been used as a salad from remotest times. Xenophon recommended it to the Persians. The Romans believe it curative of insanity. It is widely grown in Europe, America, India and elsewhere, growing best in running water with sandy bottom.

The Rose Family.—*Rosaceae*

The most important crop plants in this family are raspberry, blackberry, strawberry and dewberry. Rose and spiraea are members of the family. The resemblance between the leaves of the rose, raspberry and strawberry is quite pronounced.

All of the berries here discussed appear to have been indigenous to both the New and the Old Worlds, including Europe and Asia. Some of the largest strawberries grow wild in Chile. The North American Indians relished the raspberry as a food. Although members of this group were recognized as growing wild from ancient times, its cultivation as a garden plant appears to have commenced in the sixteenth century. It is only within the last one hundred years that special strides have been made in the development of new and improved species.

Strawberry.—*Fragaria*.—The Latin name *fraga* referred to its fragrant sweet smell. The plant was known to the Romans but not to the Greeks. Throughout all the early writings, the fact of its growth so near the ground appears to have been the feature most emphasized. It was early called the Earth Mulberry. An early German term was the earth berry (*Erd-beere*). Even the present name strawberry has a similar derivation, implying that the berries were strewn upon the ground. The old English word for strewed was strawed and one might have spoken of the strawed berry.

Like the fig, the strawberry is not a seed but a seed receptacle, the seeds being half buried on the surface.

A certain food handler always developed hives when handling crates of strawberries. The eating of fresh strawberries gave him hives but cooked strawberries did not.

Lyon has told the writer of a family with strawberry allergy in several generations. The great-grandmother had migraine from strawberries; the grandmother, "belly colic and boggy's itch"; the father, angioneurotic edema of the tongue and eyes with chills and fever; and

the patient herself had lives from strawberries. Curiously she had discovered that when menstruating she could eat strawberries without symptoms. Her daughter had urticaria, cause undetermined.*

Raspberry. Blackberry. Dewberry. Loganberry.—*Rubus*.—These are all very closely related. The dewberry can be distinguished from the blackberry by its trailing character, both the flowers and the berries tending to hang toward the ground. The loganberry is a

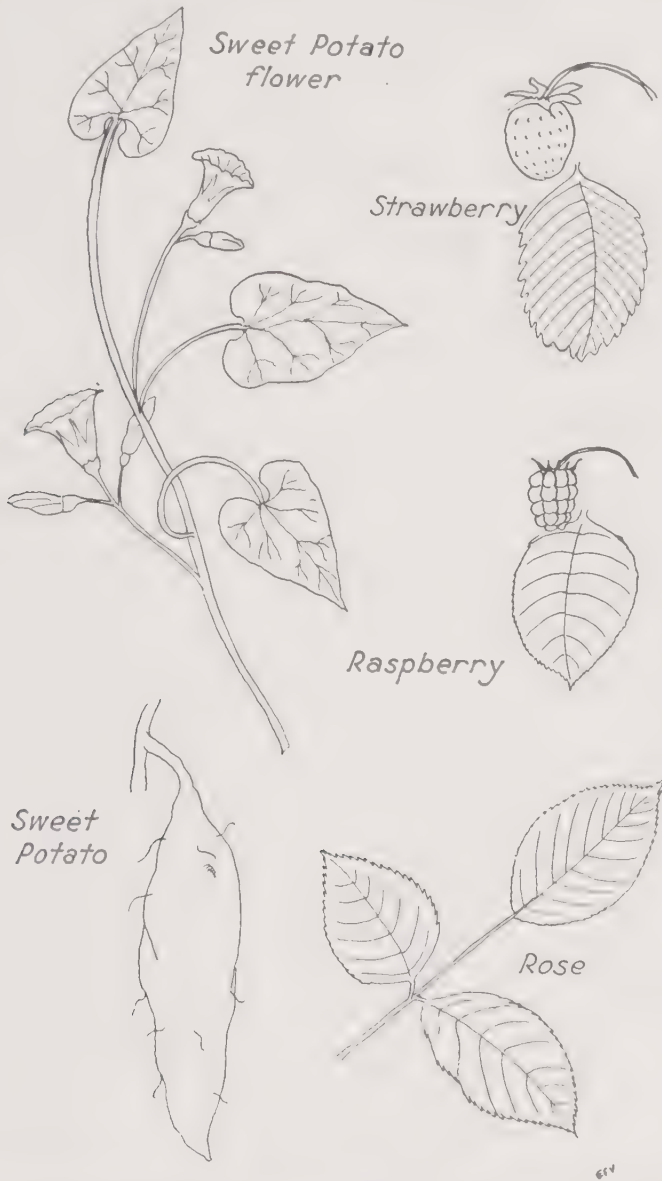


Fig. 81. The morning glory and rose families. Sweet potato with its vine and flower showing relationship to morning glory. Strawberry and raspberry, showing resemblance of leaves to those of rose.

special variety of dewberry, large, dark, almost fleshy and occasionally reaching a length up to two inches. It is cultivated widely on the Pacific Coast.

The members of this family are eaten fresh or in jellies, preserves, pies, tarts or as flavoring for beverages and frozen desserts.

The Apple Family.—*Pomaceae*

Apple.—*Malus*.—It seems improbable that this was the famous fruit of the Garden of Eden, evidence pointing more to the apricot. The apple tree grows in cooler climates, the

*Lyon, W. R., Tucson, Arizona: Personal communication.

North of Europe, China, North America. It has been cultivated from remote times, carbonized apples having been found in the habitations of the prehistoric Swiss Lake Dwellers. These may have been the original wild apples, rather than cultivated varieties. Apples were known to the ancient Romans and the Phoenicians who raised them in their gardens. They were not native to America but were imported from Europe. Today North America is the greatest apple region in the world. There are several thousand varieties.

The many ways that apple may be used in the preparation of foods make this a desirable addition for those who are not allergic to it. On the other hand, for those who are allergic, special care must be taken in its avoidance. Cider vinegar has definitely caused allergic symptoms, in my experience in patients who are allergic to apple.* Probably the chief way in which apple is often presented to the unsuspecting apple-allergic is in commercial jellies.

Pectin and jellies.—Pectin is a substance which is present in many plants, especially in fruit pulps, which thickens and jellifies on cooking. It is closely allied to the gelatins and seaweeds. It is present in large quantities in apples, cranberries, currants, gooseberries, guavas and quinces. It is deficient in raspberries, strawberries, pineapples and ripe grapes. Pectin is, therefore, added to this latter group in the manufacture of jelly. It is similarly used in jellies prepared for flavor such as mint jellies. Apple pectin or "pectin extract" is made commercially or at home from the pressed pomace, residue from cider manufacture, and from the skins and cores of apples. Pectin is also made from the inner white peel of citrus fruits.

Pectin is also used at times in some candies such as Turkish paste and gumdrops. I have seen one apple-allergic patient who experienced a recurrence of migraine following the eating of Turkish paste containing apple pectin.

Apple butter.—True apple butter consists of apple meat boiled and evaporated, with cider or vinegar, to a semi-solid consistency, seasoned with sugar and spices. It makes a pleasant extra dish for the allergic who would broaden his diet. However, it should be borne in mind that there are imitation apple butters, usually made of corn starch, flavored with citric acid and apple oil and brought to the right consistency with vegetable gums and waxes.

Crab apples.—*Malus coronaria*.—There are two varieties, one native to the United States, the other to northern Siberia. The fruit is not edible raw, the taste being harsh and acid, but when cooked it makes excellent jellies, marmalades and preserves. Crab apple is very closely related to the apple since the two have been hybridized into an edible apple. One who is allergic to apple should therefore avoid crab apple jelly.

Quince.—*Cydonia*.—Native of the Mediterranean and Caucasus regions, the quince was held in high repute by the ancients who dedicated it to the Goddess of Love. It is about the size and appearance of an apple or rounded pear, greenish in color. It is grown in many regions. Western New York is the largest growing section in the United States. The quince is not eaten raw but, like the crab apple, makes excellent jellies, jams and preserves and is very good cooked. Its pectin content is very high.

The quince was the original fruit used in the preparation of marmalades, during the reign of Henry the Seventh. The Portuguese name for quince is marmelo.

Pear.—*Pyrus*.—Native of Europe and the Caucasus, the pear, like the apple, has been found in remains of the Swiss Lake Villages. It was known to the Phoenicians, cultivated by the Romans. It was imported into the New World.

The Plum Family.—*Drupacae*

All members of this group are quite closely related, although it is probable that they did not come from common ancestors. Peach and almond contain an identical protein, amandin, which might also be found in other members of the group. So-called almond oil is obtained from almond, peach, cherry and apricot. Most of that commonly used is obtained from the apricot. Poisoning from prussic acid has occurred after the eating of peach seed and wild cherries as well as from bitter almond. The glucoside amygdalin is changed to prussic acid by an enzyme which becomes active in the presence of water. In the manufacture of almond oil the seeds are ground and pressed to remove undesirable fatty oils, following which the residue is again ground, fermented and steam distilled. The distillate is almond oil and hydrocyanic acid. The latter is removed by treatment with lime and copperas.

As is true with so many of the botanical food groups, it is not unusual to observe sensitization to two or several members of the family in a given individual, but rare to observe sensitization to all members.

*H. J. Heinz Company prepares a white vinegar derived from rye, barley and corn

Peach.—*Prunus persica*. This plant was introduced into Asia Minor and later, Greece and Rome from China, its original home. It reached Europe about the third or fourth century B.C. In Greece at that time it was supposed to have come from Persia and was spoken of as *persica*, a term from which modern "peach" is derived. It was introduced into the New World through Mexico by the Spanish conquerors.

Peach is mentioned in the books by Confucius 500 B.C. and its cultivation in China has been traced back to one thousand years before Christ.

There are over one thousand varieties of peach in the United States.

Nectarine.—This is a variety of peach with a smooth skin. While it has only recently become more frequent on the market, it is by no means a new plant. It was first described in 1532.

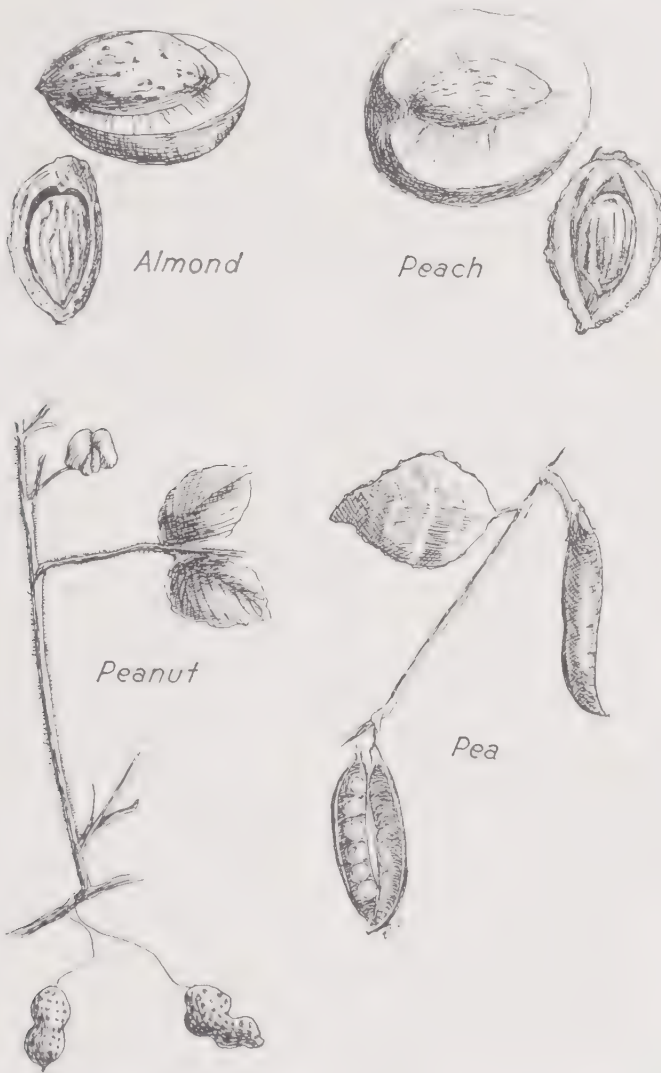


Fig. 82.—Two unrelated nuts. Almond is a member of the peach family while peanut is a legume. Resemblance to their related foods is apparent.

Apricot.—*Prunus armeniaca*. A native of Armenia, Arabia and the upper portions of central Asia, apricots were held in such high esteem that, according to Disraeli, Tradescent in 1620 joined a crusade against Morocco for the sole purpose of stealing apricots to import into Britain. The culture of apricots in England dates from that time.

Almond.—*Prunus amygdalus*.—The almond tree as well as the seed rather closely resembles the peach. The chief difference lies in the edible fleshy covering which in the almond is thin, dry, woolly, almost leathery. The tree was indigenous to Asia and to North Africa and was well known to the Hebrews, the Phoenicians, the Greeks and Romans. Almond oil has been discussed above.

Plum.—*Prunus*.—This branch of the family came originally from the Caucasus Mountains and has been cultivated for at least two thousand years. There are many

varieties. A prune is not only a dried plum. Prunes may also be fresh. A prune is any plum that can be cured or dried without removing the pit. Other varieties of plums which bear mention are the green gage named after a clergyman, Gage, who introduced it into England; the damson, a small dark plum often used for preserves; and the sloe or black-thorn, sometimes used in the preparation of gins and liqueurs.

Although the plum originated in the Old World, there is a native American plum, of rather poor quality which, however, was highly prized by the Indians.

Cherry.—*Prunus avium*.—Cherry, like so many other members of this family, took its origin in the Caucasus. It was brought to Italy by Lucullus following his victory over Mithridates. Within 120 years thereafter the cherry tree had been imported into lands as far away as Britain. Disraeli, however, remarked that "to our shame it must be told that these cherries from the King of Pontus' City of Cerasuntis are not the cherries that we are now eating; for the whole race of cherry trees was lost in the Saxon period and was only restored by the gardener of Henry VIII who brought them from Flanders."

Maraschino cherries are leached, bleached, dried, candied, and artificially flavored.

The Legumes.—*Leguminosae*

This group and the group of the cereal grains constitute the two most important agricultural crops. The three important food members are peas, beans and peanuts, but two additional members, clover and alfalfa, are at times of allergenic importance. The pollen of these latter may cause pollinosis especially in farmers who are intimately exposed to these insect pollinated plants. At times, clover honey, even alfalfa honey, may cause food allergy.

Both the Old World and the New World have contributed to this very important food group. Peas, lentils and some varieties of beans found their origin in Eurasia. The soy bean which is of increasing importance at the present time comes from China. The lima bean, kidney bean, and peanut constitute the contributions from the New World.

There is frequent crossed reaction among members of this group which sometimes includes peas, beans and peanuts and even also soy bean. Peanut appears to be a most frequent offender.

Lentil.—*Lens esculenta*.—This is probably one of the earliest plants brought into cultivation by man. The lentil was known to the Hebrews, Greeks and Egyptians and has been found in Egyptian tombs of the twelfth dynasty, 2200 to 2400 B.C. It was also present in the Swiss Lake Dwellings. Today it is cultivated through central and southern Europe, the Near East and India. In France it is used widely, especially the small red or brown lentil which is made into soups. There is a lentil flour employed in the preparation of bread.

Bean.—*Phaseolus*.—There are a number of varieties of bean, the most commonly used in this country being the lima and the kidney bean. Lima bean is a native of the New World, probably of Brazil where the variety grows wild. While it is cultivated today in many parts of the world, it does not grow wild elsewhere. Seeds have been found in the mummy graves of Peru.

Kidney bean is likewise cultivated everywhere but took its origin from America. The early explorers of North America found that the Indians cultivated it regularly in a number of varieties. The fact of numerous varieties of the cultivated form indicates that cultivation must have been going on for a very long time. The Indians used it as a food, alone, or in combination with their other highly cultivated plant, corn, in the form of succotash.

The lima bean is flat and slightly kidney shaped. The kidney bean is smaller, thicker and takes its name from its shape. It is the haricot of the French and the frijoli of Mexico. In this group are included navy beans, red beans, and Boston beans. String beans, also called snap beans or French beans, are the immature pods of several kinds of kidney beans. They are picked so young that the seeds are barely visible. Blackeye pea is a small bean native of Jamaica.

Bean flour consists of pulverized dried ripe beans. Bean sprouts is an oriental dish usually obtainable in Chinese restaurants in the United States consisting of fresh young sprouts of the mung bean, picked just before the development of leaves.

Parlato has reported sensitization to the fave bean, a bean grown extensively in southern Italy, Sicily, Sardinia and to a slight extent in Louisiana and California. Exposure to its pollen has produced severe symptoms.

Soy bean.—*Soja bean.*—*Soja max.*—This is an Asiatic bean which has been used by the Chinese as an important food for many hundreds of years and which has recently been imported into the United States where it has found a number of most important uses.

Its antiquity in China is suggested by the records of Shen Nung who sowed "the five cereals," 2800 B.C. These five cereals so important to the Chinese were rice, wheat, two varieties of millet and the soja bean.

The soy bean contains large quantities of protein and fat, practically no starch. Therefore, when it is used as an important dietary article it should not be considered as a substitute for other vegetables, but rather for meat. It may be considered more as comparable to cheese. Indeed, a soy bean cheese is commercially available.

The uses to which soy bean may be put are truly surprising. From it there is made tofu, a cheese resembling cottage cheese; soy, a brown sauce which is used in Chinese restaurants and is a constituent of Worcestershire Sauce; miso or soy bean milk, a strained water solution of the pulverized bean which looks much like cow's milk and has been used in this country as a milk substitute in infant feedings and for allergies sensitized to milk; soup noodles; jellies and sweet meats. Soy bean flour is used in the preparation of soy bread. Being high in protein, very low in carbohydrate, it is available not only for allergies but also for diabetics.

Soy bean milk which has rather high fat content is used by bakers, confectioners and chocolate manufacturers. The soy oil keeps the bread soft, apparently fresh, longer. In chocolate it tends to prevent graininess. Therefore, when one is eating bread or a chocolate bar he may be getting some soy bean.

Probably the chief soy bean product is the oil. It may be used with foods in the same manner as other high class vegetable oils. It is used in the manufacture of such diversified products as soaps, lubricants, water-proof goods, linoleum, celluloid, rubber substitutes, printing ink, paints and varnishes and as a lubricant.

Duke (1934) in stressing the importance of soy bean as a possible allergen remarked that soy bean flour is used for 250 or more purposes. It is often mixed with flour and therefore found in many breads. It is not infrequently a constituent of breakfast foods, diabetic foods, cakes, muffins, biscuits, infant foods, crackers, noodles and macaroni. It bestows on the latter the rich color which is normally found in the higher grade semolina macaroni. It is used in coffee substitutes, condensed milk, confections and sausage. It is used for fodder and fertilizer. It may be obtained as canned beans and in salads. The oil is used as a substitute for butter, lard and salad oil.

Duke found that 5 workers in a soy bean mill, who had cough and asthma, were allergic to soy bean extract. He finds that among allergies soy bean reactions occur in about the same proportion as those to peas, beans and the other legumes and appear to be part of a group reaction. Hill has found that babies fed soy bean as milk substitute not infrequently give positive skin reactions to soy bean but he usually finds no evidence that they are clinically sensitive to it.

Pea.—*Pisum*.—The pea is traced to remote antiquity. There was a Sanskrit name for the plant. It has been found in Egyptian tombs. It was cultivated by the Romans. However, until the sixteenth century when it began to be more widely cultivated in gardens it appears to have been considered an inferior plant. By 1695 it was a great delicacy and very expensive. A writer of that year said, "It is frightful to see persons sensual enough to purchase green peas at the price of fifty crowns per litron." Madame de Maintenon wrote in 1696, "This subject of peas continues to absorb all others, the anxiety to eat them, the pleasure of having eaten them and the desire to eat them again, are the three great matters which have been discussed by our Princes for four days past. Some ladies, even after having supped at the royal table and well supped too, returning to their own homes, at the risk of suffering from indigestion, will again eat peas before going to bed. It is both a fashion and a madness."

Peas were not introduced into England until after the arrival of the Monks following the Norman Conquest. They were planted in America at the time of Columbus' second voyage.

Peanut.—*Arachis hypogaea*.—The peanut is native of tropical America. The seed has been found in jars taken from the mummy graves of Peru. It is now grown in the southern United States, especially Virginia and the Carolinas, Central America, Africa, Brazil, the Orient and elsewhere. It has an unusual method of growth. The flower stalk which holds the very young peanut pod and which has grown up into the air gradually bends downward after the flower has wilted, finally touching the earth and burrowing into the soil. After it has penetrated underground the pod swells and develops into the peanut pod and seed (peanut). The peanut is not truly a nut. It might better be designated by two of its other names, ground pea or goober pea.

Its value was not recognized until the Civil War when soldiers discovered that the nuts made excellent food. Today the peanut is used as a nut, in candy manufacture, as

peanut butter, peanut oil and peanut flour. Peanut butter is made from roasted, skinned, degermed peanuts. The peanut meal or flour consists of ground peanuts from which most of the oil has been extracted. It is used in bakery for the preparation of macaroons and bread and is used widely in confectionery. Peanut flour bread is very popular in France and Germany. High grade cold pressed peanut oil makes as good a salad oil as any.



Fig. 83.—Flax.

The Flax Family.—*Linaceae*

The only member of this family which is at times used as a food is flaxseed. Flax is a native of Europe and the Orient and is now grown in most parts of the world. The plant has been in cultivation since remote history, having been shown to be the fiber used for the preparation of cloth which was used in wrapping Egyptian mummies. It is mentioned frequently in the Bible. The Greeks used it at least 700 years before Christ. Flax was being grown in Russia about A.D. 960, in Ireland A.D. 500, and was introduced into England

in 1175. It was introduced into New England with the earliest settlements. The flax fiber is used for the manufacture of linen which is woven into cloth and made into thread, yarn, twines, etc. Belgian flax is especially fine for making linen. Belgian linen and Belgian lace are world famous.

Flaxseed.—The Greeks and Romans used flaxseed as a food and it is still eaten, roasted, by the Abyssinians. Native Indians of Bombay use it as a food. Even today flaxseed occurs as a constituent of some foods. It is present in the breakfast foods, Uncle Sam's Health Food, Roman Meal, and Malt-O-Meal. Allergy to each has been reported. The writer has described one such case in which a young woman developed angioneurotic edema of the tongue and mouth so promptly after putting the first spoonful of a flaxseed cereal into her mouth, that she was unable to swallow it. Had she succeeded in doing so she probably would not have survived. Bowman and Walzer have suggested the possibility of exposure to flaxseed allergen in the drinking of milk from cows which have been fed upon flaxseed meal. The farmer allergic to flaxseed must not handle flaxseed meal used as stock feed. It is often a constituent of chicken feeds. I have seen several cases in which asthma in persons allergic to flaxseed was due to the chicken feed rather than to allergy to feathers.

A person who is allergic to flaxseed must not be given a flaxseed poultice. Flaxseed tea, made from an infusion of the covering of the seed, has been used in cough syrup. Flaxseed is rather frequently used in beauty parlors, in shampoos and especially in wave setting lotions.

Linseed oil.—Although linseed oil is not used as food, it seems appropriate to discuss it at this point. The oil of the linseed or flaxseed is used for very many purposes. From thirty to forty per cent of the seed is oil. It is used as a base for paints, varnishes and furniture polish, printing ink, lithographic ink and as a constituent of carron oil. Linoleum is linseed oil which has been hardened by treatment with sulfur chloride and exposure to heated air. The trade name is obviously derived from this, meaning oil of linum, the botanical name for flax. Rowe states that the dust from decomposition and cracking of linoleum may cause allergic symptoms. This oil treated in very much the same way is used in the preparation of oilcloth, imitation leather, waterproof materials such as oilskin coats and as a substitute for India rubber.

The oil is at times an ingredient of hair tonics and depilatories.

The Citrus Fruits.—*Rutaceae*

Here is one group of fruits which was unknown to the ancient Greeks and Romans. Botanists are of the opinion that all members were derived from a common ancestor and that the original habitat was tropical Asia and the Malay Peninsula. Small wild members of the family have been found in South America but the cultivated varieties have all been derived from southern Asia. A few members of this, the Rue family, with inedible fruits are native of the United States, chief of which are the prickly ash, hop-tree and torchwood. The fruit of the orange tree and other members is a modified berry in which the rind has developed as a whorl of modified leaves that have grown about the carpels, to surround them entirely. Citrus fruits are grown only in those parts of the United States where there is a continuous growing season and where freezing rarely occurs. The orange which is so common a constituent of our daily diet was once a most expensive luxury. When oranges were first imported into England in 1290, the Queen of Edward I bought seven.

Citron.—*Citrus medica*.—Originating in the mountains of India, this greenish lemon-like fruit was gradually carried westward through Arabia and Palestine and introduced into Italy in about the first century A.D. It is grown chiefly for its rind which is candied and is frequently seen in this country in cakes and preserves. The unripe fruit, small greenish yellow, is the etrog used in many Hebrew communities in the celebration of the Feast of the Tabernacle. Its rind is not the source of the oil of citronella, which is obtained from a fragrant Ceylonese grass.

Orange.—*Citrus sinensis*.—The sweet orange was not cultivated in Europe until about the middle of the fifteenth century. It is stated that in 1548 Juan de Castro, a Portuguese sailor, planted a tree at Lisbon. This tree was still alive in 1823 and from it practically all European orange trees were propagated. According to another authority in the year 1500 there was only one orange tree in France, planted in 1421 and still living

in 1860, at Pampeluna in Navarre. The introduction of the orange and other citrus fruits after the citron, into Europe, is attributed to the Arabs. It was brought to the New World at an early date.

The tremendous orange industry in California dates from 1873 when Mrs. L. C. Tibbets received two young trees from Bahia, Brazil, which she planted in Riverside, California. A few years later she was selling grafting-buds at a dollar apiece. In 1880 the California crop of navel oranges was one crate. Today its value runs into millions of dollars. One of Mrs. Tibbets' original navel trees is still bearing.

Much of the world's supply of orange oil comes from Sicily where it is pressed from the peel. It is used in perfumes, soaps, flavoring extracts, and slightly as a drug.

Oranges are frequently colored artificially. Allergy to this orange color dye has been reported. Oranges artificially colored are labeled accordingly.

Sugar orange.—**Seville orange.**—**Sour orange.**—**Bitter orange.**—**Bigarade orange.**—This was the original orange of Europe, being imported into Spain by the Moors in the eighth century, seven hundred years prior to the arrival of the sweet orange. It is too acid and too bitter to be eaten raw, but is grown widely through southern Europe and used principally in the manufacture of orange marmalade, and candied orange peel. The oil is also used.

Orange blossoms are sometimes used in beverages especially in South America. The use of orange blossoms by brides is an ancient custom originated by the Saracens as an emblem of happiness and prosperity.

Tangerine.—*Citrus nobilis* var. *deliciosa*.—First cultivated in Cochin China. A small variety of the mandarin orange.

Bergamot.—*Citrus bergamia*.—This first appeared in Europe in the seventeenth century. Its oil is used in perfumery. The name is also applied to certain herbs of the mint family.

Lemon.—*Citrus limonia*.—This also was introduced into Europe following the Arab conquest. Lemons are usually picked green, the time for picking depending upon the standard size desired. The fruit continues to ripen and develop its yellow color after picking, a process which requires several months. This may be hastened by exposure to a temperature between 90 and 95 degrees Fahrenheit, when the proper color may be obtained within four to six days. Lemons are used fresh, or the juice may be kept for some time. Lemon oil obtained from the peel is an important by-product. Most is made in Sicily and in southern France. Lemon extract is second only to vanilla extract in quantity consumed. This is obtained from the oil.

Grapefruit.—**Pomelo.**—**Shaddock.**—*Citrus grandis*.—There are several varieties, those in the United States consisting of the white pulped and the red pulped. This is native of Polynesia and the Malay Archipelago. It is found, possibly native, in the Fiji Islands. It was introduced into Florida by the Spaniards early in the sixteenth century. Its name is derived from the fact that the fruit grows in grape-like clusters. Superior cultivation and the development of better types have made it preeminently an American fruit.

Lime.—*Citrus aurantifolia*.—A pleasing variation from the lemon, used chiefly for flavoring beverages and confections.

Limequat.—A hybrid of the kumquat and the Mexican lime which possesses the taste of the lime and the hardness of the kumquat.

Kumquat.—**Fortunella.**—This is grown chiefly in China and Japan. The fruit is the size of a cherry or gooseberry. The entire fruit including the rind may be eaten. Sliced or quartered it may be incorporated in fruit or nut salad. It may be candied or preserved as jelly or marmalade. Although the tree may grow to a height of ten or twelve feet, in China and Japan it is often potted and dwarfed to two or three feet. This is the form in which it is more often seen in this country. (See Fig. 92.)

Pistachio.—*Pistachia vera*

Pistachio nut.—*Pistachia vera*.—This is derived from a tree native of western Asia but it is now cultivated in all countries bordering the Mediterranean and to a certain extent in California. The fruit is about the size of an olive. The kernel which is oily and mild is eaten as a nut. It is also used especially in ice cream and confectionery.

The Maple Family.—*Aceraceae*

Sugar maple.—*A. saccharinum*.—Maple sugar may be obtained from several species of maple including silver, Norway, red or swamp maple, but the chief source is the rock or sugar maple. This is native to North America, extending from Canada to Georgia and Arkansas, but especially abundant in New England. The Indians made sugar from the sap of the tree prior to the advent of the white man and the early New England colonists found it the chief and often only source of sugar.

Today most maple syrups, even though coming from Vermont, contain other sugars in addition to maple. The Vermont Maple Cooperative pure maple sugar, "cube form" (Essex Junction, Vermont) is pure maple sugar.

The Grape Family.—*Vitaceae*

The three most important genera of this family are grape, pepper vine and the genus which includes Virginia creeper and American ivy.

Like so many others of the foods which we have been discussing, the European grape or wine grape was native of Asia. As is equally true of the other foods discussed, this does not mean that there were no other types of grapes elsewhere. Indeed, there have been wild grapes native of every continent including Australia and many of the larger islands. But most of these are still wild, inedible or not as good food as the cultivated. With this food as with others, at some particular place in the world in remote history, an especially good variety was discovered and cultivated artificially, with resulting improvement. This variety was then imported into new population centers and became the edible food even though wild varieties of the same plant may previously have existed in the new areas.

Grape.—*Vitis*.—This sequence is especially interesting to follow with the grape since there are two varieties that have been developed for food, the wine grape which was brought to the United States from Europe, more remotely from Asia, and the table grape which is native to America and was imported into Europe. According to Robbins the European grape which is propagated from stem cuttings has been grown in this manner, vegetatively, for over five thousand years.

The wine grape passed from Asia into Greece, then Sicily, was carried to the south of France by the Phoenicians and on to the banks of the Rhine by the Romans. The care of vineyards and process of wine making were described in Egypt 2440 B.C. In the Bible they are mentioned in the history of Noah. This grape vine was carried to the New World by Columbus in 1494. It was introduced into California by the Spanish priests around 1769.

The European or wine grape is grown successfully in this country only in California. It is at the same time a very excellent table grape, being sweeter, larger, more tender and of more solid pulp than the native American grape. The so-called malaga grape is an example. Only the wine grape is appropriate for making raisins.

The best native American grapes are grouped under the general term fox grapes. These are the fruits that were seen by the Norsemen when they reached the New England shores in 1006 and which led them to name this newly discovered land Vinland.

The northern fox grapes like the Concord, Catawba, Delaware and Niagara are not as sweet as the wine grape but are as delicious and are used almost exclusively for the manufacture of grape juice and grape jelly. The southern fox grape is quite different. Its chief variety is the scuppernong, which grows from the James River south.

Grape Seed Oil.—This is used in Europe for culinary purposes and closely resembles olive oil.

Raisins.—These are made from the European or wine grape. Persons allergic to grape should bear in mind that dried currants are actually a special variety of grape. (See currant.)

Wine.—There are two general varieties, dry wines and sweet wines. In the former the grape sugar has been converted into alcohol through fermentation. In the latter some or most of the sugar remains, the process of fermentation having been terminated by the addition of alcohol. The coloring of red wines is derived from the skins. White wines are made from white grapes or from colored grapes with colorless juice and with skins removed. Wines contain yeast in addition to grape juice.

Brandy is the distillate of wine. Cognac is an especially famous brandy, so named after the district where it was originally made.

Grape vinegar.—This constitutes an alternative vinegar for those who are allergic to apple. There are white and red vinegars depending upon whether they are made from white or red wines.

The Mallow Family.—*Malvaceae*

Members of this family occur in a variety of forms: herbs, shrubs, and trees. The mallows are rich in mucilage. Familiar members of the family are the marsh mallow or althea, hibiscus, hollyhock and cotton.

Marsh mallow.—*Althaea officinalis*.—This is a plant native to Europe and Asia which grows chiefly in marshes near the sea. From the roots a tasteless colorless gum is obtained for the manufacture of mucilage and at times medicinally as a demulcent. Candy marshmallows were originally made from it but they are now made from sugar, corn syrup, and gelatin.

Cottonseed.—*Gossypium*.—Cotton is native to tropical Asia. Cottonseed oil is distinctly a new food. Up until 1855 it was considered chiefly a waste product. With the development of improved methods for decorticating the seed, the oil became available. It is used as a substitute for olive oil and marketed under such names as salad oil, table oil, sweet nut oil. Wesson Oil is a pure cottonseed oil. It is as nutritive as olive oil. It is sometimes used as an adulterant of olive oil. The person allergic to cottonseed oil who can take olive oil should specify virgin olive oil. Cottonseed oil is also used in the manufacture of oleomargarine and lard substitutes such as Crisco and Snowdrift. Cottolene is a mixture of refined cottonseed oil and beef suet.



Fig. 84.—Okra.

This oil is used extensively for packing sardines, salmon, mackerel, tuna and other products. It is used to a limited extent in soap manufacture.

Cottonseed flour.—This is made from the ground whole cotton seed but is not recommended as a flour substitute because of the occasional toxic effect of its gossypol. Heating destroys this toxic substance but this procedure is not consistently reliable.

Sensitization.—Aaron Brown reports that 2 per cent of allergies are skin test positive to cottonseed. Cooke finds a lower incidence of 0.6 per cent. G. T. Brown reports 2.4 per cent. Taub raises the incidence, in 246 allergies, to 5.3 per cent.

The cottonseed allergic is likely to give an extremely strong test reaction. For this reason it is safer to use the scratch test and sometimes dangerous to test intracutaneously. Taub reports a constitutional reaction following an intracutaneous test in a dilution of 1/1,000,000, requiring 2 cc. of adrenalin for relief. This patient gave a positive test reaction to 1/10,000,000.

It is stated that there is a botanical relationship between the cotton plant and the kapok tree. Certain of the excitants are identical in the two. According to Coca and Grove, cottonseed contains kapok allergen plus certain other allergens. Therefore kapok allergies usually react to cottonseed. Not all cottonseed allergies react to kapok. Taub states that cottonseed allergies also manifest a tendency to react to other seeds and nuts and to members of the pea bean family. Since there is no close botanical relationship I wonder whether this may be due to the coincidence that salted peanuts and other nuts are usually fried in cottonseed oil.

There is an easily understandable difficulty in listing the constituents of prepared lards and similar materials. The constituents are often different in cold weather and hot weather, fats of high melting point being used in the summer, low melting point in the winter. One firm in one year is said to have used 11 different fats and oils in their prepared lards. There are 189 different brands of shortening which contain cottonseed oil, either alone or mixed with other fats.

Okra.—Gumbo.—*Hibiscus esculentus*.—This is native of tropical Africa and is now grown as a vegetable in many of the warmer countries. The long tapering finger-like pods may be served whole or sliced. They are used especially in soups to give a slightly mucilaginous consistency. It is commercially available, canned. Okra seeds constitute one of the best available coffee substitutes.

A woman experienced urticaria from handling okra from her garden. The eating of okra caused gastrointestinal symptoms. A man experienced urticaria from contact with okra and with squash.

Chocolate. Cocoa.—*Theobroma cacao*

Chocolate is a contribution from the New World, Mexico, the West Indies and elsewhere. It is now grown also in British West Africa, Brazil, Ecuador, San Domingo and Venezuela. Cortez first knew of cocoa when he was treated to the drink from gold cups in the palace of the Aztec Emperor, Montezuma. The Spaniards carried cocoa back to Spain. They kept its secret for many years, selling it at a high price, as chocolate to the wealthy classes in Europe. The word cocoa is a corruption of the Spanish cacao which is in turn an adaption of the Indian Cacauatl. The Mexican Indian also used the term chocolatl. As early as 1550 chocolate factories were scattered through southern Europe. The first factory in America was established in 1765. The cocoa tree grows from 16 to 30 feet in height. The pods are large, from 6 to 12 inches long and from 2 to 5 inches in diameter. The cocoa bean, about the size and shape of a kidney bean, is protected by many layers, from inward outward, the bean shell, slime tissue, a soft inner shell and the hard almost woody outer shell of the pod. The roasting of the bean adds flavor. It is put through several processes before it emerges as a thick oily liquid which is run into molds and allowed to cool. This is the common bitter chocolate. In sweet chocolate cocoa butter and sugar are added. Milk chocolate contains, in addition, a condensed milk or milk powder. As stated under soy bean it may contain soy bean milk and oil.

Cocoa, *Theobroma cacao* or breakfast cocoa, is derived from the same bean but has more of the cocoa butter or oil removed.

Cocoa butter is used in confectionery, especially in chocolate covered candies, in the drug trade and in the manufacture of toilet preparations and cosmetics. It is especially appropriate for some of these uses since it melts at about body temperature. It does not turn rancid.

A boy with dermatosis, allergic to chocolate, who had never had asthma, developed bronchopneumonia. During convalescence he ate chocolate. His cough persisted for three or four weeks. The blood showed 12 per cent eosinophilia. Chocolate was then eliminated from the diet after which the cough promptly disappeared and the eosinophilia dropped to 4 per cent. I have seen cases of dermatitis from cocoa butter applied locally, in persons who were atopic to chocolate.

Tea.—*Camellia thea*

All of the tea grown in various parts of the world appears to have come originally from China. Its first use as a beverage is hidden in obscurity. There are three Chinese traditions. According to the first some Buddhist priests steeped the leaves of a local shrub in brackish water to disguise the unpleasant flavor of the latter. They were delighted with the results. Another story is that about 2737 B.C. Chin-nung, a famous Chinese philosopher, had built a fire from the branches of the tea plant. Some of the leaves accidentally fell into the boiling water. The effect of this accidental brew was so exhilarating that he inaugurated the custom. A third account describes its use as a medicine prior to that as a beverage.

Tea was described as being used in Persia in 1633 and as a great luxury in many parts of Europe in 1647. In 1657 it sold in England at prices ranging from \$30 to \$50 per pound. It was sold in American Colonies in 1680 at from \$5 to \$6 per pound for the cheap qualities. In 1667 one hundred pounds were imported into England. In 1880, 72,000,000

pounds were imported into the United States. In the early days of the Colonies its use was widely condemned by the clergy "who felt it harmful to health, morals and public order."

The stimulating effect of tea is due to its caffeine content, the average cup containing approximately 1.5 grains, the same amount that is in an average cup of coffee. Caffeine is present in both tea and coffee. One who is hyperergic to caffeine may be unable to take either beverage, but one who is allergic to tea or coffee is not necessarily allergic to the other.

The Carrot Family.—*Umbelliferae*

Members of this family are usually herbs. They grow best in the north temperate regions, rather poorly in the tropics. As foods they are grown chiefly for their leaves or roots, although the seeds of celery, caraway, fennel and coriander are often used as flavoring, and make important additions to our list of spices.

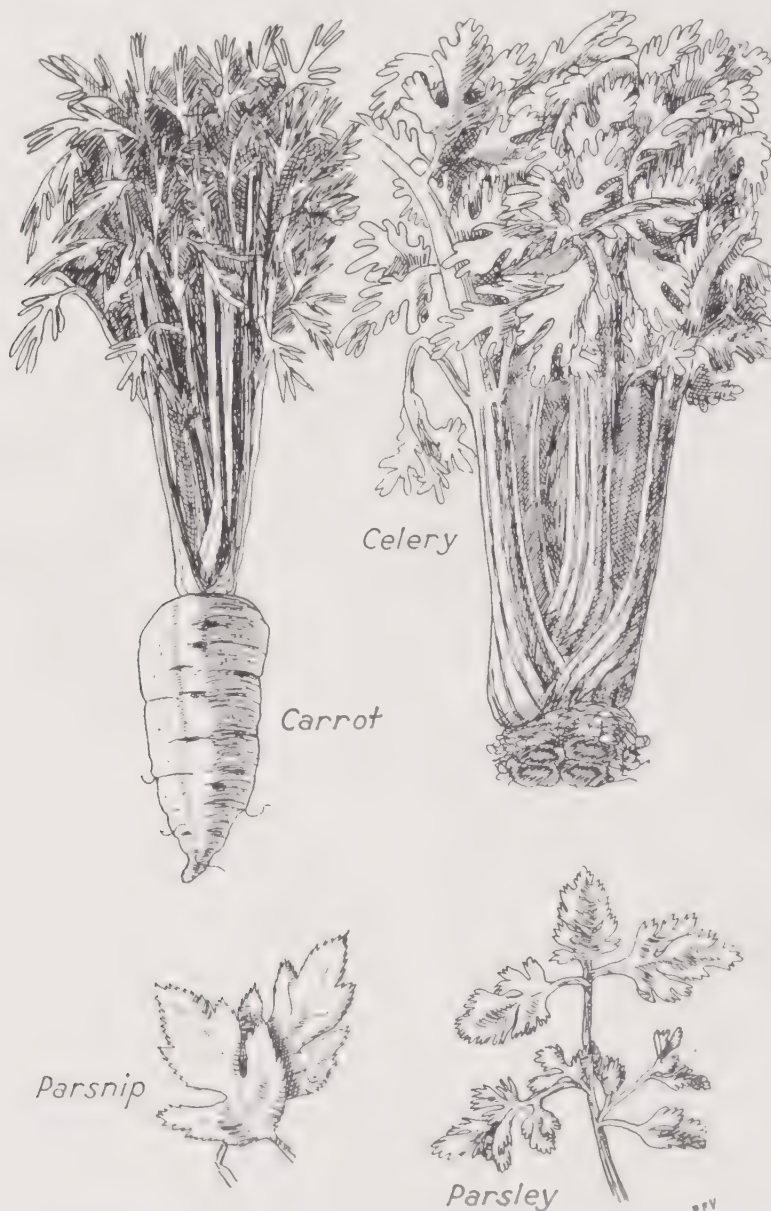


Fig. 85.—The carrot family. Note resemblance of leaves, in contrast to other families illustrated.

Carrot.—*Daucus carota*.—This plant, native of Europe and western Asia, reversed the procedure common to so many plants previously described in that it was imported into the Far East. It reversed what appears to have been the more common direction. In India it was described as having been imported from Persia and it was brought into China at the

beginning of the fourteenth century. The ancient Greeks knew it only in the wild variety but the Romans of the first to the third centuries A.D. spoke of it as a garden plant. Here again, however, instead of France obtaining the plant from Italy and Asia Minor, Italy is said to have imported it from France.

Carrot is most often served cooked, but tastes best when eaten raw like celery. In this form it has a slightly nutty flavor which is delicious. Its high provitamin A content is due to the coloring matter carotene. The juice of the red carrot is sometimes used on the farm as coloring matter for butter.

Parsnip.—*Peucedanum sativum*.—Like the carrot, parsnip is native of Europe. Also like the carrot, the edible portion is a tap root. Again, like its cousin, the ancient Romans employed the wild plant medicinally before the cultivated varieties were known as food.

The Emperor Tiberius was so fond of parsnips that he had them imported annually from Germany, where the culture appears to have been started. There is a wild parsnip indigenous to western North America, the roots of which are the size of peanuts and which was widely eaten by the Indians. The cultivated parsnip was imported from Europe early in the period of colonization.

Parsley.—*Carum petroselinum*.—A native of Europe, this leafy food was highly esteemed by the Greeks and Romans. Pliny, Galen and many others wrote of it. It was introduced into England from Sardinia in 1548.

It adds flavor to soups and broths and contains an essential oil which is mildly stimulating. When eaten with onions it is said to take off the onion smell and prevent the after taste. It is used chiefly as a seasoning and garnish.

Only the cultivated varieties should be used since the wild or "fool's parsley" is poisonous. One variety of parsley, Hamburg or tulip-rooted parsley, has an edible root similar to a small parsnip.

Celery.—*Apium graveolens*.—Native of Europe, celery was mentioned in Homer's *Odyssey*. It was known to the ancients, but only as a medicine. It was recommended as a blood purifier. Sturtevant suggests that the emphasis placed on the rapidity or celerity of its beneficial action may well be the origin of its common name. It was not eaten as a table food until the sixteenth century.

Every part of the plant may be used in food. The stalks and heart may be eaten raw, plain or with fillings; they may be used in salads and may be cooked. They are often used in soups. The leaves may be used as garnish and for celery-salt.

Celeriac. Turnip rooted celery. **German celery.**—*Apium graveolens rapaceum*.—This is cultivated more in Europe than in America. It has a large edible turnip-like root.

Fennel.—*Foeniculum vulgare*.—A plant cultivated by the ancient Romans, resembling asparagus in appearance, the leaves of which are used in sausage, the stalk eaten in salads, and the seeds used in confectionery and in flavoring of liquors.

Caraway seeds.—*Carum carvi*.—Like so many members of this family the fruit or seed of the caraway plant is highly aromatic and is used for its spicy flavor. Caraway seeds are used in baking, especially in rye bread, in confectionery, and as a culinary flavor. In Holland they are also used in certain types of cheese. The essential oil is employed in perfumery and soap making. Kümmel is an alcoholic liquor, a distillate from caraway seed.

The roots are edible, superior to parsnip and are still eaten in northern Europe. The young leaves make a good salad while the larger ones may be boiled and eaten as a spinach.

The antiquity of the plant in Europe is established by the fact that caraway seeds have been found in the débris of the lake habitations in Switzerland.

Coriander.—*Coriandrum sativum*.—The seeds were used as a spice by the early Hebrews and Romans. The plant was used in medicine and cookery in Britain prior to the Norman Conquest. The seeds have been found in Egyptian tombs of 1000 B.C. It was described in China A.D. 500. The seeds and leaves are used for the same purposes as the caraway seeds.

Aniseed.—*Myrrhis odorata*.—This again is used for similar purposes. Anisette, a famous French liqueur derives its chief flavor therefrom.

Oil of anise is used in chewing gum and in a preparation for cleaning artificial dentures. Severe allergic stomatitis has been found to be due to these two contact substances.

Dill.—*Anethum graveolens*.—Mentioned in the New Testament writings, and known to the Romans, dill is used for the same purposes as caraway. It rather resembles fennel in appearance. The seeds are used in the manufacture of sausage and pickles while the leaves which have a flavor resembling fennel and mint are used for the same purposes as mint leaves.

Dill pickles are made from cucumbers. Flavor is added by the use of dill seed, allspice, black pepper, coriander seed and bay leaves.

The Laurel Family.—*Lauraceae*

Cinnamon.—*Cinnamomum cassia*.—The cinnamon tree is a member of the laurel family, somewhat resembling English laurel in appearance. The inner bark, sold in the form of quills, possesses the fragrant aromatic flavor responsible for its popularity in cooking. It is native of Ceylon and was known to the ancient Hebrews, Greeks and Romans but was not cultivated on the shores of the Mediterranean at that time. It was carried to these regions by the Arabs who kept its source secret for several centuries. That it grew wild in Ceylon was not known in Europe until the fourteenth century despite the fact that it had been used for nearly one thousand years.

Avocado. Alligator pear.—*Persea gratissima*.—The tree is indigenous to tropical America. It is now widely grown in the West Indies, Mexico, Central America, northern South America, Florida and California. Like the laurel, the tree is an evergreen.

The fruit is often pear-shaped but it is not a pear. The flesh is rich, nutlike, rather buttery, and rather tasteless at first, although it has a taste which grows on one. It is best served as a salad dish with lemon juice, lime juice, or especially with grapefruit.

The name avocado has resulted from the Spanish mispronunciation of the Indian "Ahuacatl."

Bay leaves.—*Laurus nobilis*.—This is yet another member of the laurel family. The bay leaves are the aromatic leaves of the sweet bay or laurel tree. This plant grows wild in Mediterranean countries and in the southern United States. There is no connection with bay rum which was originally distilled from the leaves of the bayberry. The bay leaf or laurel leaf is familiar in Greek history as emblematic of heroism. It is used today as a flavoring for soups, broths, etc.

The Huckleberry Family.—*Vacciniaceae*

This family grows widely from tropical to arctic regions. It is closely related to the heath family which latter includes wintergreens, teaberry, the American laurel, Labrador tea, azalea, rhododendron, and trailing arbutus. The two important culinary members of the huckleberry family are huckleberry and cranberry.

Huckleberry. Blueberry. Bilberry.—Indigenous to North America and a favorite food of the Indians, it is now used in preserves or cooked in muffins or pies.

Cranberry.—*Vaccinium macrocarpon*.—There are two varieties, the large cranberry, native of North America and growing wild in bogs from Virginia to Wisconsin, and the small or Old World cranberry, native of alpine and subarctic regions of Asia and Europe. Both are grown for food but the American is preferred. The first attempt at artificial cultivation was on Cape Cod in about 1840. Cape Cod, New Jersey and Wisconsin supply most of the market cranberries today. The soil must be peaty or alluvial with an abundant underground supply of water.

Cranberry probably derived its name from the appearance of the flower. According to Robbins, "Just before the flower opens the pedicel, calyx, and corolla resemble the neck, head and bill of a crane."

The Olive Family.—*Oleaceae*

This includes 21 genera and 500 species, best known of which are the olive, lilac, privet, jasmine and ash.

Olive.—*Olea europaea*.—A native of the Mediterranean region, this tree has been cultivated from earliest history. In the United States it is grown chiefly in California. It is not to be confused with the so-called Californian olive, native to North America, a form of mountain laurel, which does not produce an edible fruit. The edible olive of California is an imported tree. There are trees near Nice and Genoa which are believed to be more than 2,000 years old. The California trees were planted by the Franciscan Fathers in pioneer days.

Ripe olives constitute a nutritious food. Green olives are more of a relish. Pickled olives may be either green or ripe. The method of pickling varies in different localities, being done with brine only, or with salt and vinegar, or with the addition of fennel and thyme or coriander, laurel leaves, etc.

Olive oil.—There are several varieties, chiefly Italian, French and Californian. The Italian is a heavier oil with more of the taste of the olive. The French has a lighter taste and is preferred by many. The California oil is equally good. Virgin oil is the best quality olive oil, made from hand-picked fruit and consisting of only the first-run oil, originally extracted by pressing the pulp. More oil is later extracted by subsequent treatment of the pressed pulp with hot water and high hydraulic pressure. This is known as olive oil "foots." It is used in the manufacture of castile and some other soaps and as a lubricant.

One cannot be certain that oil labeled as olive oil is pure olive oil even though the word "pure," the Italian flag, foreign language or names or pictures, or the designation "virgin" appears on the container, or if it is labeled as imported. Cottonseed and tea-seed oil are the commonest adulterants although peanut and corn oils are also used. Color is often achieved with coal-tar dyes. No person allergic to olive, corn, peanut, almond or cottonseed oil should use ready-prepared mayonnaise, since these oils are used interchangeably, the selection of the moment depending upon market prices.

The Morning Glory Family.—*Convolvulacae*

The only members of this family that are widely known are the morning glory and sweet potato. The sweet potato vine, with its flower, closely resembles the morning glory. They are not at all related to the Irish potato which latter is much more closely related to tomato. Native of Central and South America, the sweet potato is now grown in most tropical and subtropical countries including southern Europe, the southern United States, India, the Indian Archipelago, Hawaii, New Zealand, Tahiti and the Philippines.



Fig. 86.—Detail of sweet potato leaf and carrot leaf. Note difference between the former and that of Irish potato.

Sweet potato. *Ipomoea batatas*. The sweet potato is a fleshy root containing large quantities of starch, as contrasted with the Irish potato of which the starchy tuber is a stem. This plant is a valuable food. Flour, starch, glucose and alcohol are minor by-products. A food flour is made from it in the Orient. A Japanese sweet potato candy which can easily be made in this country consists in rolled, mashed, boiled sweet potato balls which have been tossed into boiling sugar syrup that is ready to "sugar," where they are allowed to cook until brown. After removing and cooling they become crisp.

Sweet potato pie, scarcely distinguishable from pumpkin pie, is a pleasant dessert dish available for those allergies who are not sensitized to its constituents.

Yams.—The yam of the southern United States is a watery sweet potato. It is rich in sugar and becomes soft and gelatinous when cooked. This is altogether different from the true yam or Chinese potato which belongs to a family closely related to the lily. The latter has never been successfully cultivated in this country.

The Mint Family.—*Labiatae*

Mint.—*Mentha*.—This includes peppermint, spearmint and pennyroyal, all native of Europe, Asia and northern Africa. Pennyroyal has fallen into disuse. Both it and spearmint were known to the ancients. Peppermint was first described in 1724. Peppermint and spearmint are cultivated chiefly for their oils which are used in candy manufacture and for other flavoring purposes. The mint leaves are used as seasoning. Fresh mint jelly may be made with gelatin but the commercial preparation is flavored apple jelly.

Sage.—*Salvia officinalis*.—This is an ancient condiment mentioned by the Greeks and Romans, still in use, especially in poultry dressing, sausages, and less so in the flavoring of pork, soups, sauces and cheese. It is a shrub. The leaves are generally used.

Savory.—*Micromeria juliana*.—Native of the eastern Mediterranean region, this is a small herb the leaves of which are used like sage.

Thyme.—*Thymus vulgaris*.—A member of the same family, native of Europe, an herb the leaves of which are used for seasoning.

The Potato Family.—*Solanaceae*

This includes such apparently unrelated plants as tomato, Irish potato, red and green peppers, tobacco, belladonna, eggplant, thorn apple and petunia. Not only do the Irish potato leaves and those of the tomato closely resemble each other but the fruit of the former looks very much like a miniature tomato. They resemble each other so much in these respects that one would expect to find evidence of frequent allergic crossed reaction. On the contrary, both the writer and Withers have found this decidedly less frequent than among some of the other food groups. This suggests that they may not have had a common origin, a probability which is further strengthened by the fact that they have never been successfully hybridized. The superficial resemblance of tomato and Irish potato is evidenced on study of the cross section of the fruit and is further seen in similar sections of the red and green peppers and eggplant.

Irish potato.—*Solanum tuberosum*.—Native of the mountainous regions of Chile and Peru, this plant was unknown in Mexico at the time of the discovery of America. It was carried from South America to Europe whence, later, it was introduced into the North American Colonies. It grows best in cold regions, the best potato growing in the states of the Union being those along the Canadian border and in the Rocky Mountains. This undoubtedly accounts for the fact that though it was a food of the South American Indians, its cultivation did not spread directly through tropical America and North America. Potatoes are said to have been introduced into New England by an Irish Colony in 1719. Sir Walter Raleigh had planted them on his estate in Ireland in 1585.

Although the sweet potato is a fleshy root, Irish potato is an underground stem. It is actually a tuber or growth on the stem. One of the latest theories is that this tuber is a gall or irritation growth associated with the presence of certain fungi. Orchids likewise develop tubers when the stem or root is infected with the proper fungus. According to Robbins the fungus appears to stunt the growth of the terminal bud and cause the development of hypertrophied cells. "When the potato was first introduced into France, it was found that when tubers are planted, a crop was produced, but when the seed was sown no tubers were obtained. From this it was inferred that when tubers were planted they infected the new ones, while the seed, free of fungi, did not furnish a supply to infect the stolons, and hence tubers could not form. However, no difficulty is now experienced in securing tubers from seed because the soil has become inoculated with the proper fungi. If this theory is correct a potato tuber is in reality a gall, produced by a foreign organism." Like the tomato the Irish potato has the habit of "running out." A new variety produces for a number of years and then degenerates. New varieties are therefore appearing on the market at intervals.

The potato is of great importance to those allergies who are sensitized to the cereal grains. Potato flour or potato starch is readily available. A palatable bread may be made

by mixing pure rye flour and potato flour. It is employed to some extent by sausage makers, bakers, and confectioners. However, in this country corn starch has taken its place in great measure. Very excellent angel food cake and golden cake may be made with potato starch. (See discussion of wheat substitutes.)

Potato chips or Saratoga chips are thin slices of potato fried in boiling lard or oil. Cottonseed oil is often used. They were first introduced by a colored chef at Morris Lake, Saratoga, N. Y.

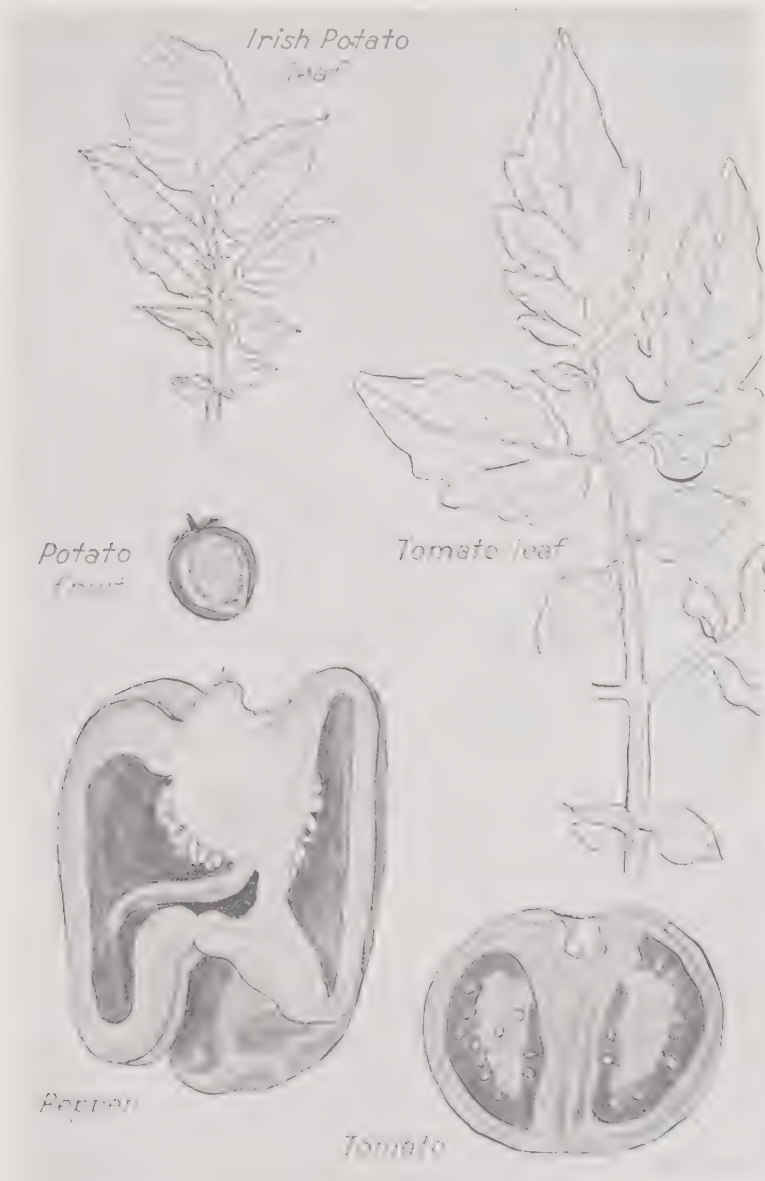


Fig. 87.—The potato family.

Potato syrup is used widely in Europe in the same way that corn syrup is used in this country. Similarly, potato sugar is available especially in Europe.

Tomato. Gold apple. Love apple. *Lycopersicon esculentum*.—Although wild varieties of this type of fruit grow elsewhere, as indicated by the discovery of wild tomatoes in interior Africa in 1860, the cultivated variety which is so well known today was found by the early explorers, in use by the natives of Mexico and South America. From there it was carried to Spain and southern Europe where it was used as a food long before its value was recognized in the United States. Jefferson mentions tomatoes as being grown in Virginia in 1781 but it was not until the period from 1812 to 1844 that they came into use in this

country as a food. The Secretary of the Connecticut Board of Agriculture wrote, "We raised our first tomatoes about 1832 as a curiosity, made no use of them although we had heard that the French ate them. They were called love apples."

This failure to appreciate the value of the tomato was probably due to two factors. First there was a prejudice against them, probably due to the fact that they were related to the deadly nightshade, which is poisonous because of its stramonium content; and second because until within recent years this fruit was by no means as good to eat as it is today. Like the potato the tomato tends to "run out" and new varieties are appearing in the market from time to time.

Botanically the tomato is a true berry.

Tomato is an excellent food, high in vitamin content and as is well known, is used in a great variety of ways. Tomato paste is an Italian preparation of the pulp, freed from skin, core and seed and concentrated by evaporation. It is a standard canned article useful in making sauces, for serving with spaghetti and other foods and flavoring soups, broths, etc.

Rohner (1937) grafted a section of tomato plant on the stalk of a potato plant. With this he succeeded in growing tomatoes above ground and potatoes underground.



Fig. 88.—Varieties of peppers. This does not include the biologically unrelated black pepper or white pepper.

Peppers.—*Capsicum annuum*.—Although these were widely grown in all parts of the world the preponderance of evidence is that all cultivated varieties took their origin from the New World. There are no ancient Sanskrit or Chinese names for the plant. Columbus imported it into Spain in 1493. Its culture in the New World was carried on by the Aztecs prior to the discovery of America and before then by the Toltecs. The early explorers remarked that this was the only condiment known to the native Indians.

There are many varieties of capsicum, the commonest being ordinary red pepper, cayenne pepper, paprika (now grown chiefly in Hungary and Spain) and tabasco (grown from the long fruited Mexican pepper).

The fresh vegetable peppers are mild flavored fleshy capsicums of the Spanish pimiento type, the type from which paprika is also obtained.

The Mexican chili is the long fruited strong pepper. The name is derived from what is probably the original source of the plant, Chile.

The numerous varieties differ in the degree of pungency. This latter is due to a crystalline nitrogenous compound, capsaicin. The pungency is in the fleshy part of the fruit as well as in the seed.

The red pepper is to be distinguished from black and white pepper which grows from an entirely different botanical plant. Pepper is a constituent of catsup, of Mexican tamales and is usually found in pickles and salads. Chili con carne is a mixture of small ground peppers and meat. Green peppers and red peppers differ only in that the latter have ripened

Eggplant. Jew's apple. Mad apple.—*Solanum melongena*.—This food derives its name from its resemblance in shape to an egg. Like the tomato it is a true berry botanically. Unknown to the ancients, the cultivated variety probably originated in India. It was first described in Europe about the ninth century, although Avicenna, the famous Arab physician, knew it in the sixth century. The earliest record in China dates from the fifth century.

Coffee.—*Coffea arabica*

This invaluable dietary constituent was contributed by Abyssinia, on the east coast of Africa, where it has grown wild since earliest times. The African natives ate the raw grain as a stimulant rather than making an infusion or drink. The warriors mixed pulverized roasted beans with fat, molding them into balls which they carried with them as food on their trips. From Ethiopia the culture of this evergreen bush was carried into southern Arabia by the fifteenth century. This Arabian coffee was usually shipped through the port of Mocha. From Arabia knowledge of it spread to Egypt and Constantinople in the sixteenth century, to Venice in the seventeenth century and to England shortly thereafter. At the latter time coffee houses, where one would go to drink coffee as one now goes to drink alcoholic beverages, sprang up in London, Paris, Vienna, and the other European centers and smaller cities. This is the origin of the present term cafe. Coffee was denounced by religious zealots as being an intoxicating, insidiously pernicious drink.

It was not until the beginning of the eighteenth century that the Mocha coffee found any serious competition. In 1706 coffee-growing was successful in Java. It is now grown in other islands of the East and West Indies and in Central and South America. Today Brazil is the world's greatest producer of coffee.

The red coffee berry as it grows on the tree reminds one slightly of the holly berry, although it is about twice as long and oval in shape. The bean is covered by two layers, an inner parchment layer and an outer fleshy one. After these are removed the coffee is roasted. Roasting produces certain very important changes. The bean becomes larger, lighter in weight and brown in color due to the conversion of sugar to caramel. A volatile oil, caffeol, is developed during roasting and it is the chief source of the aroma and flavor. Roasting also frees the caffeine from its combination with tannin, and makes the oils more readily soluble.

One may be hyperergic to caffeine. This is the type of person whom coffee makes nervous or sleepless. One may be allergic to coffee, reacting with any of the characteristic manifestations of food allergy. I find this not an infrequent sensitization.

Finally one may be allergic not to coffee but to one of the adulterants which are sometimes found in the cheaper grades. The adulteration of coffee was formerly such a common procedure that the housewife customarily purchased her coffee in the bean and ground it at home, thus assuring herself of its authenticity. Many substitutes were formerly used as adulterants, chief of which were chicory, beans, peas, carrots, cereals and chestnuts. The pure food laws have done much to improve this situation. However, chicory is still widely used with coffee, especially in Europe, where the flavor of an infusion of coffee bean and chicory is actually preferred to that of coffee alone. Many foods have been used, not as adulterants, but as substitutes for coffee where the latter is not available. Examples are: asparagus seeds, date seeds, horse chestnut, okra seeds, dandelion roots, chicory, beechnut.

The name coffee is derived from the Turkish Kahveh, meaning an infusion.*

The Gourd Family.—*Cucurbitaceae*

The principal edible members of this family are the pumpkin, squash, melons and cucumber. That some of them are quite closely related biologically is indicated by the fact that cucumber and cantaloupe contain an identical protein, cucurbitin. It is not infrequent to find persons allergic to both of these members of the family and often also to others.

Squash. Pumpkin. Gourd.—*Cucurbita pepo*.—The term squash is applied to many varieties of edible gourds, the best known of which is the pumpkin. The winter squashes and those with harder shells are usually called gourds while the softer ones are squashes. Although the first site of cultivation is uncertain, the general consensus is that squashes are of North American origin. Certain it is that the pumpkin was cultivated in the fields with corn by the Indians before the arrival of Columbus, just as it is today.

*The Franck Tablet (The Franck Chicory Company, Bay City, Michigan) consists of roasted ground chicory, no coffee.

Vegetable Marrow. This is a variety of squash, of the pumpkin family. The term is used often in England.

Cucumber.—*Cucumis sativus*.—This, like other members of the family, grows on creeping vines. The plant, native of Asia and Egypt, has been in cultivation since remote times. It has been grown in Asia for 3,000 years. It was brought from China to the West about 100



Fig. 89.—Leaves of cantaloupe, cucumber, and squash.

B.C. It was known to the ancient Greeks and Romans. The Emperor Tiberius who appears to have been very much of an epicure had cucumbers at his table every day. Columbus carried the plant to Haiti in 1494. It was being grown in Virginia in 1584.

Pickles, or pickled cucumbers, are cut green, the time of harvest depending not upon ripeness but upon the size. The gherkin is a Jamaica cucumber but the term is applied to others used for pickling. For a discussion of dill pickles, see Dill in the Carrot Family.

It has been said above that cucumber and cantaloupe have an identical protein and that there is frequent evidence of allergic crossed reaction. Robbins states that although the impression is general that cucumbers can be crossed with the melon, experiments have shown that this cannot be done.

Watermelon.—*Citrullus vulgaris*.—Contrary to customary belief this is a product of tropical Africa. However, under American culture it has done unusually well. It was grown in Egypt prior to Exodus. It is still a most important fruit of that country. It was imported into North America very early during colonization.

One who is allergic to watermelon must also be cautious to avoid watermelon rind pickle.



Fig. 90.—Angioneurotic edema of face (cheek and eyelids) from eating cantaloupe.

Cantaloupe. Muskmelon.—*Cucumis melo*.—Native of the Old World tropics and possibly known to the ancients, it was not fully described until the sixteenth century, when its perfume and exquisite taste were lauded. It seems probable, therefore, if it did exist during the time of the Romans it had not yet acquired its delicious flavor. It cannot be said with certainty that muskmelons were not grown in America prior to the arrival of Columbus, since he did find them growing in the West Indies at the time of his second voyage (1494).

Sensitization.—Melons being seasonal, the patient himself often suspects their allergenic importance. When symptoms are lowgrade, mildly sensitized persons may experience symptoms at the beginning of the season which disappear later, or vice versa. One patient, for example, developed urticaria and diarrhea at the commencement of the watermelon season. After two or three days of eating them he no longer had trouble therefrom. Another described his response as follows: "I suspect that watermelons don't agree with me. The symptoms aren't bad, but I start the season eating watermelon and end it not eating them."

The Thistle Family.—*Compositae*

This is one of the largest families of the plant kingdom with 10,000 species and about 760 genera. The members are mostly herbs, although there are a number of shrubs and a few tropical trees. Many weeds which are allergenic on account of their pollens, causing pollinosis, belong to this family. Owing to the wide variety of species one would not expect frequent evidence of crossed reaction among foods in this family. However, Grubb and Vaughan have observed frequent group reactions among the pollens of flowering plants such as ragweed, goldenrod, dandelion, daisy and sunflower.

Lettuce.—*Lactuca sativa*.—Native of Europe and the Orient, this, the best of all salad plants, was known to the Persian Kings in 550 B.C. and was described by Hippocrates, Aristotle, Dioscorides, Galen and Pliny. Chaucer wrote of it in England about 1440. It was transported to North America and Brazil at an early date. The habit of lettuce to head up was firmly established by the sixteenth century.

Salsify.—**Oyster plant.**—*Tragopogon porrifolius*.—This is grown for its fleshy roots which have somewhat the flavor of oysters. They are used cooked or as a relish. They may be served boiled like asparagus, fried like oysters or stewed like carrots. The roots thinly sliced may be used in salads.



Fig. 91. Lettuce (romaine) and artichoke. Both members of composite family.

Native of the Mediterranean region, it was not mentioned in the literature of kitchen garden culture until the sixteenth century.

Endive.—*Cichorium endiva*.—A plant first cultivated in India and known to ancient Egypt and Greece, this is grown chiefly for its leaves which are used in salads. The time of its first introduction into the United States was uncertain, but it was before 1806.

Chicory. *Cichorium*.—Native of Europe and the Orient, this plant probably grew wild in the days of ancient Greece and Rome and was not described as being a cultivated plant until 1616. Its leaves are used in salads, the young roots are edible in a form like parsnip, and the larger roots are used as an adulterant for coffee. These latter, about ten to fourteen inches long and two inches in diameter, are white and fleshy but when roasted turn brown like coffee. They contain no caffeine nor tannin but do contain a bitter principle in a volatile oil. Roasting produces an aroma. As a beverage chicory is rather more bitter than coffee.

Jerusalem artichoke.—*Helianthus tuberosus*.—This is a member of the sunflower family. The name Jerusalem is a corruption of the Italian for sunflower, *girasole*, meaning "turning with the sun." It is native of North America, probably of the Mississippi Valley, and was cultivated by the Indians. The edible portion is a root tuber. It somewhat resembles the

potato. It is sweetish and rather more watery. There are two varieties, long with red skin and round with white. They may be boiled, pickled, made into soups or eaten raw as a relish. The food value is not high.

Artichoke.—*Cynara cardunculus*.—This is the cultivated form of the cardoon, native of the Mediterranean region and known to the ancient Greeks and Romans. It is a plant which resembles a large thistle, cultivated for its flowering head, growing upon a long stem. The bases of the fleshy leaves and the bottoms of the flower heads are edible and delicious. The plant is mentioned especially because canned artichoke hearts which are readily available are an excellent substitute dish for allergies.

Dandelion.—*Taraxacum*.—Although rather ignored in this country the dandelion is cultivated in hothouses in France chiefly for the fresh young leaves which are highly regarded for salads. Roasted dandelion roots have been used as a coffee substitute.

Miscellaneous

Brazil nut. Niggertoe.—*Bertholletia excelsa*.—The tree from which this nut is obtained is tropical (Brazil, Venezuela and Guiana) and is not closely related to any of the other food plants. The nut was first described in 1808. These familiar triangular nuts grow in large, very hard, seed vessels which resemble the coconut in appearance and size. The triangular state is due to the flat facets or contact surfaces of the nuts inside the shell. Twenty or more are found in one shell.

Caper.—*Capparis*.—The flower bud of the caper bush, of the Mediterranean countries and India, is used as a pickle and added to sausage. It is not closely related to other foods. Capers are available, usually pickled, in glass bottles.

Cashew nuts.—*Anacardium occidentale*.—The Cashew tree, native of Central America and northern South America, is not closely related to other food plants. It is now cultivated also in the West Indies, the Indian Archipelago and eastern Africa. The writer has observed allergy to cashew nuts in a young girl who developed asthma and urticaria each time she ate them.

Clove.—*Eugenia caryophyllata*.—The clove tree is an evergreen, member of the myrtle family, native of the Moluccas in the East Indies. The familiar clove spice is the unexpanded flower bud. The stalk is also used, chiefly for adulterating ground cloves. For many years the Dutch had a monopoly on this product but is now grown also in Zanzibar, Dutch and British East Indies and in the West Indies. While the Dutch held the monopoly they refused to sell except when bids reached the prices set by the government. Later, when surplus crops were released, some of the barrels were found to be nearly a hundred years old and about to fall to pieces but the cloves themselves were in excellent condition. Oil of cloves is a common culinary article.

Guava.—*Pisidium guajava*.—Native of tropical America, and another member of the myrtle family, the guava produces a fruit which varies from the size of a plum to that of an apple and resembles an orange. It makes excellent preserves, the best known of which is guava jelly.

Allspice.—*Pimenta officinalis*.—The allspice tree is cultivated in the West Indies. The name does not indicate a mixture of spices but rather a special spice which in taste resembles a combination of cinnamon, cloves, and nutmeg. The seed of the allspice or "pimento tree" is about the size of a small pea and is picked when fully grown but not yet ripened. It is dried in the sun. It is not the true pimento (see Peppers, red and green).

Elderberry.—*Sambucus nigra*.—This is the fruit of the elder bush or tree customarily used in the manufacture of elderberry wine and, in Portugal, for coloring port wine. It is not closely related to other foods. It is a member of the honeysuckle family.

Licorice.—*Hedysarum mackenzii*.—Native of Russia and central Asia, the licorice plant is a distant relative of the legumes. Licorice is obtained from the dried root. The name is a corruption of the genetic name glycyrrhiza, derived from the Greek, meaning "sweet root." It is used as a candy, medicinally, in plug tobacco, some liqueurs and in porter.

Nutmeg.—*Myristica fragrans*.—The nutmeg is native of the Dutch East Indies. It was first described by the Arabian physicians of the Dark Ages and at that time was imported overland into Europe. The fruit resembles the peach, with a similar longitudinal groove on one side. When ripe the outer portion bursts into two pieces exposing the enclosed seed which is covered by a bright red aril, the mace of commerce. The seed has a hard outer shell. The nutmeg of commerce is inside the shell. Nutmeg is grown in a number of tropical countries, but the best comes from the Banda Islands in the Dutch East Indies.

Mace.—*Myristica fragrans*.—This is the inner covering of the shell of the nutmeg. It is blood red and fleshy. Preparation for the market consists in flattening and drying.

Pepper (Black and White).—*Piper nigrum*.—The pepper bush is not closely related to other food plants. This condiment was mentioned by Roman writers of the age of Augustus. Attila the Hun required 3,000 pounds of pepper as part of the ransom of the City of Rome. A climbing shrub, the plant is indigenous to southern India, the Malay Peninsula and adjacent islands. The fruit is a small round berry, the "peppercorn." Black pepper consists of the entire unripe berry. White pepper, from the same plant, is obtained after removal of the dark outer shell of the berry. It is less pungent but has a better flavor.

Vanilla.—*Vanilla planifolia*.—This is a climbing vine of the orchid family, native of Mexico, where Cortez was first introduced to it as a flavoring in a cup of chocolate given him by the Aztec King, Montezuma. The plant is now grown in both the West Indies and the East Indies, and elsewhere, but the best still comes from southern Mexico. The vanilla orchid vine twines itself about trees, rocks, shrubs, etc. From each blossom a pod develops which grows to 6 to 10 inches in length and resembles in appearance a cross between a large string bean and a thin banana. The dried pod is the true vanilla bean from which genuine vanilla extract is made.

Vanilla extract is an alcoholic extract of the bean. There are imitation vanilla extracts, made with synthetic vanillin.

Vanilla powder or vanilla "sugar" is usually sugar or a mixture of starch and sugar, or calcium carbonate flavored with vanilla or synthetic vanillin. It is used in ice cream manufacture and is usually considered preferable since it yields more flavor in the extreme cold.

Mango.—*Curcuma amada*.—A fruit believed to be native of tropical Asia which is now grown in most tropical and subtropical countries including Mexico, the West Indies and Florida. A mango varies in size from a plum to a cantaloupe and its flesh is eaten usually with a spoon. It is available canned and preserved. There are many grades, the best being quite delicious. Kirby Smith has described contact dermatitis from mangos.

Maté.—*Ilex paraquensis*.—This consists of the leaves and young shoots of a species of holly grown in South America, used as a beverage instead of tea. It is prepared in the same way and like tea and coffee contains caffeine and tannin. An average of more than 120,000,000 pounds are exported annually from Brazil. It is prepared and drunk like tea. It tastes like tea, possibly slightly more bitter.

Karaya.—Bullen* states that Karaya gum (*Stereulia*) is a constituent of Imbricoll, a preparation for increasing bulk of stools, in constipation. It is also in Saraka, Karaba, Karabim, Mucara, and Bassoran, similar laxative preparations.

Figley* has observed 9 positive reactions to Karaya gum in patients with eczema, asthma, perennial rhinitis and urticaria. One intentionally ate some of the Indian gum mixed with mashed potato, reacting with coryza and epigastric discomfort. Later she had another attack of coryza after eating a gelatin preparation which was found to contain Indian gum.

Figley finds it to be a constituent of many denture adhesive powders (Nyko Adherent Powder, Dr. Wernet's Powder, Dent-A-Firm Denture Powder and Stix); also in Listerine Toothpaste and Laetona Toothpaste. It is used in gumdrops and other candies with soft centers. It is widely used in several ready prepared diabetic foods including soy bean and almond wafers and in making emulsions.

Gum Tragacanth.—This gum is found in many hand and face lotions and is used in the wrappers of many cheap cigars. It is botanically and antigenically related to acacia.

Gum Arabic Acacia.—Spielman and Baldwin report allergy to gum arabic in a candy maker. His asthma commenced six months after he started working in a candy factory as a plaster molder. In this task he was exposed to dust, a large percentage of which was gum arabic. Skin tests were positive, confirmed on passive transfer. Gum arabic appears to contain a protein fraction, since the material used for testing was found to contain 0.5 per cent total nitrogen and to give a positive biuret test. Since gum arabic has been used for intravenous infusion, this observation is of importance. It is found in printer's drying spray.

Unusual and Exotic Foods

We have not yet exhausted the list of available foods of vegetable origin. There are a number of others which are rarely eaten in this country or only

*Bullen, Stearn S., and Figley, Karl D.: In the International Correspondence Club of Allergy.



Fig. 92.—Exotic fruits. Purchased in the market in New Orleans and Florida.

Top row, left to right: mandarin, sapodilla, shaddock. Middle row: chocho or vegetable pear, *monstera deliciosa*, cherimoya or custard apple. Bottom row: carambola or star apple, prickly pear, papaya.

It should be noted that enlargement in the illustration is not proportionate. Papaya, *monstera*, and shaddock are proportionately much larger than they appear.

in small areas thereof, most of which are unrelated to the groups described here, but many of which could easily be made available for allergies whose diets have been otherwise too restricted. A few of these have been unpopular because of the taste or consistency, characteristics which experience has shown can usually be surprisingly improved by cultivation. Several represent plants which have been under cultivation in this country for but a short time and which are therefore known only locally. Others are foods which must be imported from the tropics or elsewhere and with which spoilage has in the



Fig. 93.—Exotic fruits. Left row, reading down: kumquat, avocado. Middle row: plantain, guava, sugar apple. Right row: carissa, tamarind.
Plantain and avocado are proportionately larger than they appear.

past presented a material problem. However, with modern methods of refrigerated transportation and preserving and canning at the source of supply, these are difficulties which are no longer insurmountable. One need but look back even within the present generation to recall that not long since, oranges and other foods which must be transported long distances were available only "in season." Today they are available throughout the year and are no longer luxuries, but indispensable constituents of our daily diet.

Tropical and Subtropical Florida Fruits. For a number of years, imported tropical and subtropical fruits have been grown in Florida, many of which can now be added as substitutes to the allergic diet. The more important varieties are packed and shipped, on order, by Col. H. W. Johnston, Homestead, Florida. The State of Florida, Department of Agriculture, Bulletin No. 46 (1935) lists these fruits and contains a number of recipes for their use. The Agricultural Extension Service, Gainesville, Florida, Bulletin No. 85 (1936), contains botanical and technical description of the plants with numerous photographs.

Akee	Jujube
Ambarella	Ketembilla
Berries	Langsat
Dewberry	Litchi
Down Myrtle	Loquat (Japanese Plum)
Elderberry	Mamey
Gooseberry	Mamnee Sapote (Marmalade Plum)
Haws	Mango
Loganberries	Monistera Deliciosa
Mulberries	Papaya
Bilimbi	Persimmon
Bullock's Heart	Pitaya
Cacti	Pomegranate
1. Prickly Pear, Indian Fig	Pond Apple
2. Cereus	Quince
Carambola	Rose Apple
Carissa or Natal Plum	Roselle
Carob Bean	Sapodilla
Cashew	Satin Fruit
Cherimoya (Jamaica Apple)	Sour-Sop (Guanabana)
Citrus	Star Apple
Granadilla or Passion Fruit	Strychnos Spinosa (Natal Orange)
(Small Pomegranate)	Sugar Apple (Sweet-Sop)
Guava	Tamarind
Ilama	Ti-Es or Canistel or Vegetable Egg
Imbu	

An extract of enzymes derived from the papaya, sold under the trade name Tendra, has come into some use in this country as a tenderizer for the rapid aging of meats.

Sapodilla.—*Achras sapota*.—**Chicle.**—Kleinman (1935) has reported two cases of allergy to chicle, an ingredient of chewing gum. The first experienced vasomotor rhinitis, after chewing gum. Failing to react to other ingredients, he was tested intracutaneously with a concentrated chicle extract, with a resulting systemic reaction manifested by sneezing, nasal blockage, conjunctival injection, itching of the eyes, asthma and a strongly positive skin reaction. The etiologic factor was proved by repeated attempts to chew gum. The second case reacted to chicle by skin test, but since his nasal symptoms were fairly constant even though he did not chew gum, the etiologic connection was not satisfactorily established. Twenty-five control tests on other allergies and 6 on nonallergies were negative, except for one moderately positive skin reaction, with no confirmatory clinical history.

Chicle gum is the base of ordinary chewing gum. In addition, sugar, corn syrup and flavoring oils are incorporated. The commonest oils are wintergreen, peppermint and spearmint. One brand of gum also contains milk. Chicle is a solidified latex or sap of the Achias tree, native of Central and South America, British Honduras and Guatemala. Most of the chicle used in this country is imported from southern Mexico.

Substitute Food List. Foods Obtainable Through Fancy Grocers

The following substitute foods may be obtained through local grocers or from one or more of the following fancy grocers and importers: R. H. Macy Company, 34th Street and Broadway, New York.

Almond Paste	Kumquats
Anise Seed	Litchi
Apricot Juice	Loganberry Juice
Arrow Root Flour	Mace
Artichokes, canned	Marjoram
Banana Flour	Marrons Glacé
Barley Cereal	Maté (tea substitute)
Bay Leaves	Mazola (corn oil)
Brown or Ground Rice	Olive Butter (olives, sweet pepper, spices)
Canned Chinese Bamboo Shoots	Peanut Oil
Canned Chinese Water Chestnuts	Pignola (pine nuts)
Canned Frogs' Legs	Popcorn
Canned Rattlesnake Meat	Poppy Seed
Caraway Seeds	Potato Flour
Cardamon Seed	Powdered Parsley
Cassia Buds	Rice Flour
Cheeses (Sheep, goat, as listed under cheese)	Ripe Mangoes (ripe in syrup)
Chestnut Flour	Sage
Coriander Seed	Sago (Tapioca)
Crushed Dates	Samp (corn)
Fiego (coffee substitute from figs, does not contain coffee or chicory)	Savory
Goose Liver	Soy Bean Flour
Guava	Tapioca
Hollywood cup (coffee, substitute made from barley, figs and bran. Contains no coffee)	Tarragon Leaves
	Terrapin Meat
	Thyme
	Turmeric
	Wild Rice

CHAPTER XXXVIII

EDIBLE ANIMAL FOODS

In this discussion we shall follow the classification of Ellis (Table XXIX). In this as with the vegetable foods, the classification progresses from the earlier or simpler evolutionary forms: edible invertebrates, arthropods, vertebrate fishes, amphibians, reptiles, birds and mammals. While some seafoods are closely enough related to appear to give crossed reactions (e.g., lobster, shrimp and crayfish), our experience has been that one must test with as many varieties of fish as with other foods. Indeed, sensitization is sometimes remarkably specific. Thus, one man in the writer's experience develops migraine from shad but eats shad roe without consequence. This is analogous to the difference between chicken and egg.

MOLLUSCS

Food allergic persons commonly harbor a deep-rooted prejudice against molluscs, commonly called "shellfish." In our experience highly allergic individuals may eat shellfish and other seafoods provided they are not sensitized thereto. Since seafoods aid in broadening the restricted diet, especially if animal foods have been radically withdrawn, they should be included in test materials. The following discussion is in considerable detail, since information should be available concerning suitable substitute foods as well as those which must be prohibited.

Abalone is a large sea snail found chiefly along the California coast, the muscle system of which is used as food, being served in chowder to which it gives a clam flavor.

The snail has been in artificial cultivation since about 50 B.C. It is relished more in Europe than in the New World, an average of 80 million being sold each year in Paris alone. When cooked the snail looks and tastes very much like shrimp and has been unwittingly enjoyed in Europe by many Americans who had previously boasted that here was one food they could not or would not eat. The snail is a very clean animal, living on plant life. Snail culture in France is most sanitary. Snails may be procured canned and are best served as an appetizer.

Mussel.—There are fresh water and salt water varieties. The sea mussel which is the variety used as food is a bivalve shellfish. It is eaten more in France and Holland than in this country. Any recipe appropriate for oysters and clams is appropriate for mussels except that less should be used in chowders because of the strong flavor.

Oyster. This most ancient food has been cultivated in oyster beds for over 2,000 years. The tradition against its use during those months whose names contain no R is inappropriate in the United States. In Europe there is a disease among oysters in the summer months which justifies the proscription. American oysters are not affected. Another reason for the prohibition is that oysters spawn during these months. However, this is true only for the New England States. In Chesapeake Bay, the chief source of oysters, spawning occurs at any time of the year.

Scallops.—This is another bivalve, the muscle section of which constitutes the edible portion.

TABLE XXIX
ELLIS' CLASSIFICATION OF EDIBLE ANIMALS
(Condensed)

Invertebrata				
PHYLUM MULLUSCA				
COMMON NAME	CLASS	FAMILY	GENUS	SPECIES
Abalone (red)	Gastropoda	Haliotidae	Haliotis	rufescens
Snail (edible)	Gastropoda	Helicidae	Helix	pomatia
Mussel, salt water	Pelecypoda	Mytilidae	Mytilus	edulis (several
Mussel, fresh	Pelecypoda	Unionidae	Unio	sp.)
Oysters	Pelecypoda	Ostreidae	Ostrea	virginica
Scallops (common)	Pelecypoda	Pectinidae	Pecten	irradians
Clams (round)	Pelecypoda	Veneridae	Venus	mercenaria
Squid	Cephalopoda	Loliginidae	Loligo	pealei
PHYLUM ARTHROPODA				
Lobster	Crustacea	Nephropidae	Homarus	americanus
Crayfish	Crustacea	Astacidae	Astacus	nigrescens
Shrimp	Crustacea	Crangonidae	Crangon	vulgaris
Prawn	Crustacea	Palaemonidae	Palaemon	vulgaris
Crabs, Rock	Crustacea	Canceridae	Cancer	irroratus
Vertebrata				
CLASS PISCES				
	<i>Synonym</i>			
Anchovy		Engraulidae	Anchovia	delicatissima
Bass, Black		Centrarchidae	Micropterus	salmoides
Crappie		Centrarchidae	Pomoxis	annularis
Rock Bass	Goggleeye	Centrarchidae	Ambloplites	rupestris
Bluegill	Blue Sunfish	Centrarchidae	Lepomis	pallidus
Butterfish	Harvestfish	Stromateidae	Pronotus	triacanthus
Harvestfish	Whiting	Stromateidae	Peprilus	paru
Buffalo, common		Catostomidae	Ictiobus	cyprinella
Drum	Lake Carp	Catostomidae	Carpoides	thompsoni
Sucker, common	White sucker	Catostomidae	Catostomas	commersoni
Catfish, blue	Mississippi Cat	Siluridae	Ictalurus	furcatus
Channel Cat	Spotted Cat	Siluridae	Ictalurus	punctatus
Codfish		Gadidae	Gadus	callarias
Haddock		Gadidae	Melanogrammus	aeglefinus
Flounder (At- lantic)		Pleuronectidae	Glyptocephalus	cyanoglossus
Flounder (Pacific)		Pleuronectidae	Platichthys	stellatus
Halibut (Pacific)		Pleuronectidae	Paralichthys	californicus
Pike, Wall-eyed	Jack Salmon	Percidae	Stizostedion	vitreum
Pike, Sand	Sauger	Percidae	Stizostedion	canadense
Perch, Yellow	Ringed Perch	Percidae	Perca	flavescens
Pickering	Common Pike	Esoxidae	Esox	lucius
Muskellunge		Esoxidae	Esox	masquinongy
Herring, common		Clupeidae	Clupeus	larengus
Shad, common		Clupeidae	Alosa	sapidissima
Sardines	Calif. Sardine	Clupeidae	Clupanodon	ceruleus
Smelts, American		Argentinidae	Osmerus	mordaxchthys
Sturgeon, common		Acipenseridae	Acipenser	sturio
Salmon, Red	Chinook Salmon	Salmonidae	Oncorhynchus	tsacawytsha
Whitefish	Common whitefish	Salmonidae	Coregonus	clupeiformis
Lake Herring	Cisco	Salmonidae	Argyrosomomas	artedi
Bloater	Silver whitefish	Salmonidae	Argyrosomomas	prognathus
Trout	Rainbow trout	Salmonidae	Salmo	irideus
Weakfish	Sea trout	Scienidae	Cynoscion	regalis
Mackerel	Common Mackerel	Scombridae	Scombrus	scombrus
Tuna Fish		Scombridae	Thunnus	thynnus

TABLE XXIX—CONTINUED

CLASS AMPHIBIA				
COMMON NAME	SYNONYM	FAMILY	GENUS	SPECIES
Frog	Bull Frog	Ranidae	Rana	catesbiana
CLASS REPTILIA				
Turtle	Diamond back terrapin	Testudinae	Malacoclemmys	palustris
CLASS AVES				
Chicken		Gallinae	Gallus	domesticus
Turkey		Gallinae	Meleagris	gallopavo-bronze
Goose		Anserinae	Anser	anser
Duck			Anas	domestica
Guinea			Nemida	meleagris
Squab		Columbae	Columba	livia
Quail		Perdidae	Ortyx	virginiana
Grouse		Tetraonidae	Tetrae	cupido—prairie chicken
Partridge		Tetraonidae	Bonasa	nubellus
CLASS MAMMALIA				
	Order			
Beef	Ungulata	Bovidae	Bos	taurus
Beef (Buffalo)	Ungulata	Bovidae	Bos	bison—buffalo
Mutton	Ungulata	Bovidae	Ovis	aries
Goat	Ungulata	Bovidae	Capra	?
Reindeer—Caribou	Ungulata	Cervidae	Cervus	tarandus
Rabbit	Rodentia	Leporidae	Lepus	sylvaticus
Squirrel	Rodentia		Sciurus	carolinensis

Clam.—These, like oysters, may be obtained canned.

Squid.—A small species of cuttlefish, this is of the same family as the octopus. It is widely appreciated in Mediterranean countries. In North America it is used chiefly as bait. It is marketed fresh, dried or canned. Fresh, it is cooked like fish. It is said to be good, cut into small pieces which are dipped in egg batter, deep-fried in hot oil and served with stuffed dates or fried sweet peppers.

ARTHROPODS

This large group includes insects and other animals whose jointed skeleton is secreted by the skin and so is outside, not inside, the body. Several aquatic arthropods are used as food.

Lobster.—Kern tells of an allergic who could eat lobster caught north of Cape Cod but not lobster from south of that point. On investigation Kern discovered that the food supply of the latter, coming from the Gulf Stream and southern waters, is altogether different from that of the former which is derived from the Arctic Current. The patient's assertion may well be based upon more than imagination.*

The lobster of the Atlantic Coast is characterized by its large claws. The spiny lobster of the Pacific Coast differs in that it lacks the double claws, has unusually well developed antennae, and a number of short protective spines. This is the langouste of France.

Lobster is available canned.

Crayfish.—This is a small fresh water member of the lobster family, ranging from three or four inches long for the eastern and central states to six along the Pacific Coast. The edible portion is chiefly the tail muscle.

*Kern, Richard A., Philadelphia. Personal communication.

Shrimp.—Another member of the same suborder as lobster and crayfish of which the tail muscle is eaten. It may be obtained fresh or canned.

Prawn.—This is often called the southern shrimp. There is very little difference from the culinary viewpoint. The tail muscle is eaten.

Crab.—Hard shell and soft shell crabs are the same. The growing crab sheds the hard shell. In certain seasons, before the new shell has hardened it may reach the table as a soft shell crab. In the latter case the entire crab including shell is eaten. Canned crab meat is available.

FISHES

BY DR. CAROL LANE FENTON

The fishes belong to the vertebrates, or animals with backbones, and so are not related to "shellfish." Indeed, the fishes themselves are not one group, but include several different classes whose significance may be best understood by a survey of their evolutionary development.

Evolution.—We can discover the earliest ancestors of fishes only by inference, since they had no bones and so did not become fossils. They probably were much like the lancelet, or *Amphioxus*, a creature two or three inches long with a rod of gristle down its back, but no vertebrae. Lancelets bury themselves in the sand under shallow salt water. They are caught near the island of Amoy, South China, but most of the catch is eaten locally.

Some zoologists think the next stage is represented by the lamprey, an eel-shaped creature that has no jaws, and no fins which are arranged in pairs. Its mouth forms a sucker with which it fastens itself to fish, whose flesh it eats with a rough, protrusible tongue. Other authorities regard the lamprey as a degenerate relative of the extinct ostracoderms, which are the oldest of fossil vertebrates. Ostracoderms possessed no jaws; some had heads that were covered with scales, but the heads of others were encased in thick plates of bone. The skull was bony in some forms, but cartilaginous in others. Their wide bodies suggest that most ostracoderms wriggled on the bottom instead of swimming freely.

Sharks and their relatives form the lowest, most primitive class of vertebrates that properly are called fish. They have jaws and two nostrils; most of them also possess paired limbs in the form of pectoral and pelvic fins. Aside from these characters, however, there is little similarity among divisions of the class. Modern sharks are torpedo-shaped animals with sharp teeth, cartilaginous skeletons and powerful swimming tails. Skates and rays have wide bodies, flat teeth, and slender, even finless tails. Various ancient sharks had bony skeletons, jaws resembling those of a turtle, or thick armor on the head and fore part of the body. Sharks resembling those of modern times, but much larger, were abundant during the Tertiary age. Their petrified teeth are frequently found in Tertiary deposits of the Atlantic Coastal Plain.

The bony fish (*Chondrichthyes*) get their name from their skeleton, which is well ossified except in a few degenerate forms. They appeared while armored sharks were rulers of the sea; though unimportant for millions of years, they now dominate the fish world. They are divided into three subclasses, the ray-fins, fringe-fins, and lungfishes.

The ray-fins seem to include the most primitive members of the bony fishes, as well as the most modern. The primitive sorts had a sharklike tail, with the backbone extending to the tip of the upper part, or lobe. Instead of typical scales, they possessed bony plates much like those of some ancient sharks. The sturgeon is a survivor of this group, as is the paddle fish of the Mississippi and Chinese rivers. In the sturgeon the bony skeleton has largely degenerated into cartilage, while the skin plates are arranged in five longitudinal rows that only partly cover the body.

The garpike has progressed somewhat further. With its ancient relatives, it has developed highly enameled skin plates and has shortened its backbone, which no longer enters the tail. The tail fin, like fins on the body, is supported by rays of bone which spread out like the ribs of a fan.

Lungfishes have single or paired lungs which are really highly specialized swim bladders. These fish once were common in the sea, but they now inhabit ponds and streams that dry up every year. Before this happens, the lungfish coil up in cocoons of mud, where they breathe air until water returns. They also breathe air when they find themselves in foul water.

The fringe-fins are almost extinct. They had rays which were arranged like fingers on fins whose basic skeleton was bony, and their backbone extended into the tail. There seems to be no doubt that some members of this group also developed lungs. They used their paired fins as legs, took to land during dry spells, and so turned into amphibians that resembled salamanders. All this happened some 320,000,000 years ago, during the Devonian age. Since that time, the fringe-fins have accomplished little in evolution.

The freshwater dogfish, better called bowfin, is a primitive ray-fin which is prized as a game fish. It is rarely used as food except in the South, but the flesh is palatable when properly cooked, and is excellent smoked.

The true dogfish is a small shark. Large amounts of dogfish meat are sold as grayfish; though coarse, it has an acceptable flavor. Thousands of pounds of meat from large species of sharks are sold under the name of swordfish, a misnomer which should be readily apparent to anyone who knows that the swordfish is a bony fish related to the mackerel and tuna. Indeed, most of our food and game fishes of both salt and fresh water belong to the bony class.

Classification of Fishes

Paddlefishes (Polyodontidae)	Butterfishes
Sturgeons (Acipenseridae)	Basses (Centrarchidae)
Catfishes (Siluridae)	Crappie and Calico Bass (Shad)
Suckers (Catostomidae)	Rock Basses
Buffalo Fishes	Sacramento Perch
Carp Suckers	Warmouth Bass
Chub Suckers	True Sunfishes
Redhorse and Freshwater Mulletts	Black Basses
Minnnows (Cyprinidae)	Perches (Percidae)
Chub	American Pike-Perches
True Eels (Anguillidae)	River Perch
Tarpons (Elopidae)	Sea Basses (Serranidae)
Tarpon	Striped Bass
Herrings (Clupeidae)	White Perches
True Herrings	Sea Bass
True Sardines	Snappers (Lutianidae)
Shad	Grunts (Haemulidae)
Anchovies (Engraulidae)	Porgies (Sparidae)
Whitefish, Salmon and Trout (Salmonidae)	Scups
Whitefishes	True Porgies
Lake Herrings and Ciscoes	Sheepsheads
Pacific Salmon	Croakers (Sciaenidae)
Salmon and Trout	Weakfishes
Graylings (Thymallidae)	Red Drum
Smelts (Argentinidae)	True Croakers
Pikes (Esocidae)	Kingfishes
Banded Pickerel and Other Pickerel	Sea Drums
Common Pike	Freshwater Drum
Muskellunge	Rockfishes (Scorpaenidae)
Mulletts (Mugilidae)	Haddock
True Mulletts	Rose-fish
Barracuda (Sphyraenidae)	Greenlings (Hexagrammidae)
Mackerels (Scombridae)	Atka Mackerel
True Mackerels	Alaska Greenfish
Frigate Mackerels	Cultus Cod
Little Tunnies	Codfishes (Gadidae)
Great Tunnies	Pollacks
Spanish Mackerels	Tomeods
Sailfishes (Istiophoridae)	True Codfishes
Swordfishes (Xiphiidae)	Haddock
Pompanos (Carangidae)	Freshwater Ling
Leather-jacks	Flounders (Pleuronectidae)
Amberfishes	Greenland Halibut
Mackerel-seads	Common Halibut
Cavallas	Sole
Moonfishes	Bastard Halibuts
True Pompanos	Winter Flounder
Bluefish (Pomatomidae)	Arctic Flounder
Dolphins (Coryphaenidae)	Starry Flounder
Pomfrets (Bramidae)	Window Pane

Allergenic Relationships. The question arises as to whether from the allergic point of view the allergenic activity of true fishes of different species is sufficiently specific that one must test with a number of varieties or whether they are all antigenically related and a single test for fish will give the desired information.

I know of no comprehensive work that has been done toward answering this question. Many persons allergic to fish have observed that one variety will cause symptoms while others may be eaten with impunity. Positive reaction to fish glue appears to be nonspecific as far as different varieties of fish are concerned. This may represent an organ-specific reaction (see discussion of feathers and of species and group specificity below). One should have at least one representative, usually the commonest, of the different biologic groups commonly eaten and should test individually with any special fish which the patient is in the habit of eating. It may be that a much smaller number of groups will eventually be found to suffice or we may find that individual testing must be done with each species. Tuft and Blumstein (1946) have shown a common antigenic relationship but there are wide variations in reaction and they advise multiple testing unless some one fish gives a very intense reaction in which event all should be avoided. The author can state that when testing with about twenty species of true fishes, some will be found to react positively while others are negative; the list of positives varies with different individuals, thus ruling out nonspecific reaction; and patients observe frequently that there is a correlation between positive reactions and their symptomatic responses.

Discussion

With individual testing we have found positive reactions to a number of fish allergens. Sardine and salmon react rather frequently, cod and halibut less so. We have observed positive reactions to mackerel, flounder, sole, shad, tuna and a number of other true fishes, proved on subsequent trial to be responsible for symptoms. One difficulty encountered is that a fish as eaten may not be the same as that used in testing even though the names are the same. Thus, weakfish is often called sea bass. A patient found positive to sole may feel that he can eat flounder, not realizing that they are the same. Perch, so-called, may be a bass (Sacramento perch); a true perch; or a sea bass (white perch). The pompano of Florida waters is essentially the same as amberfish of the Bermudas. The term chub is applied to many medium sized and small fish such as the common chub, the squawfish (a member of the minnow family), large mouthed black bass, chopas, and the Lafayette fish.

One assumes a definite risk in testing with codfish extract to determine whether a person can take cod liver oil. There are thirty species of fish which are recognized and allowable for U. S. P. cod liver oil. To be sure, they are all members of the *Gadus* family.* All members of the *Gadus* family are accepted. Cod itself is *Gadus morrhuae*. Halibut which unlike cod lies on the bottom of the ocean contains only small quantities of vitamin D but abundant vitamin A. The situation is reversed in cod liver oil. Vitamin A reinforcement of cod liver oil is usually in the form of carotene.

Balyeat and Bowen have reported urticaria, vomiting, diarrhea and eczema in children sensitized to cod liver oil. They found that carotene concentrate fortified with vitamin D was tolerated without symptoms. It is safer to test

*Stevens, Henry: Washington, D. C., personal communication.

with the preparation which is to be given to the individual and it should be borne in mind that even this varies at different times of the year.

Simmons (1938) observed 7 constitutional reactions in a total of 783 injections into 126 patients, due to sodium morrhuate given in the treatment of varicose veins, hydrocele, hemorrhoids, etc. Two of the cases had what he considered severe anaphylactic reaction.

Caviar.—The finer grades are sturgeon roe. The domestic supply is obtained both from sturgeons and from spoonbill, white fish, lake herring and carp.

It should be remembered that some fish preparation is usually present in catsup.

Sardine.—Several different species are used in the preparation of sardines but they are all of the herring family. The original sardine was a Mediterranean pilchard. The Norwegian sardine is a sprat. The American sardine is a small herring.

Miscellaneous notes.—A man with positive skin reaction to shad developed angioneurotic edema of the lips after eating this fish. He has no difficulty from eating shad roe.

A man allergic to salmon ate a salmon croquette, after which he promptly developed asthma. The cook put the croquettes in the ice box near the butter. The following day the butter tasted of salmon and he developed asthma after eating it.

Glue.—Allergy to glue while apparently quite rare is usually very severe when it does occur. Cooke has reported a death from endermal testing with fish glue. He also observed constitutional reaction to testing with a dilution of LePage's glue in a patient who experienced asthma and coryza from handling it. Duke and Stofer observed a nearly fatal reaction from scratch test to fish glue. This same patient had previously experienced severe reaction, even collapse from the licking of a stamp. She had symptoms following contact with a wet label of a beer bottle and again when handling a pair of recently repaired shoes.

Andrews and McNitt describe a severe systemic reaction with asthma from scratch test with Denison's fish glue. This was in a young woman who experiences angioneurotic edema of the tongue, lips and throat following the eating of fish, and upon contact of the lips and tongue with adhesive, stickers, labels, etc. United States postage stamps and envelopes did not cause this reaction but commercial labels and Christmas seals did. Later she began having attacks of asthma when working in the drafting room or an art school. This also was traced to proximity to glue. She was found allergic to fish glue, bluefish, codfish and salmon.

These authors believe that allergy to glue is always to fish glue, not to other animal glues. Fish glue is prepared from the waste products of cod, haddock, cusk, hake and pollack. The head, skin and trimmings are used.

Glue is not used on postage stamps but may be found on labels and the flaps of envelopes. It is used in the manufacture of furniture, in book bindings, the sizing of cloth and wall paper, in the sizing and stiffening of fabrics and in straw hats.

Apparently only two cases have been hyposensitized, the one reported by Andrews and McNitt and another treated by Gilmartin. Treatment was commenced with 1:200,000 dilution. Injections were given at intervals of 3 to 5 days, the concentration being worked up to 1:10,000. Good results were reported.

AMPHIBIANS AND REPTILES

These are so unrelated to other foods and to each other that they need be but mentioned. Frog legs and various preparations of turtle are the two most frequently eaten although canned rattlesnake meat is regularly on the market in New York.

Mock turtle contains veal, soup stock, various vegetables and spices, lemon juice, etc.

Allergy to rattlesnake venom. Ray (1934) reports the case of a man who about three years previously had been bitten by a rattlesnake. Immediately after his second bite he developed generalized urticaria and collapse, followed by a generalized desquamative dermatitis, more pronounced near the site of bite. This persisted for some time. Ray ruled out other possible factors such as dermatitis due to flora on the ranch, etc. Spangler (1931) reports two cases of allergy to snake venom. Both were cases of druggists who handled crotalin, dried snake venom. Symptoms were those of vasomotor rhinitis and asthma.

BIRDS

This family includes chicken, duck, goose, turkey, guinea hen, squab, partridge, quail, grouse and several others. They are all so distantly related genetically that group or crossed sensitization has not been observed. This is consistent with the fact that they do not hybridize. In a single genus such as that of chicken, where there are many species which do hybridize, crossed sensitization among the species appears to be constantly present.

Fowl.—If one reacts positively to the food extract of a given type of bird, this does not mean that all birds must be eliminated from the diet. Others may be eaten. It is of course possible that one will react to more than one kind of bird, as one may react to more than one kind of vegetable, but this does not indicate a group reaction. The different types of fowl used as food must be tested separately.

Feathers.—The same appears not to be true in allergy to feathers. There appears to be some tendency toward group reaction to feathers such as those from chicken, duck, goose, turkey, canary, and pigeon. This has not been investigated conclusively, due in part to the fact that feather extracts have not been as reliable as those of the animal danders and pollens.

The evidence has been chiefly empiric, based on observation of the results of ordinary skin testing and the patient's response to exposure. Thus, patients found allergic to the types of feathers used in their pillows may also experience symptoms from exposure to canary feathers or pigeon feathers. Again, persons may react positively by skin test to two or more feather extracts while failing to react to extracts of the flesh of the corresponding birds. Such persons may experience inhalant allergy from the feather dust but can eat the flesh with impunity.

It seems probable that the antigen in feathers is rather more specific for feather, any type, than for the protein of the source-bird. Such organ specificity resembles that of the crystalline lens. Lens protein is anaphylactogenically identical in different species and genera and is not the same as the body protein of the animal from which it was obtained. Lens protein is lens protein no matter what its source.

Alpha and beta crystallin, the two proteins of the crystalline lens, are organ specific rather than species specific. An animal sensitized to beef serum will not react to beef crystallin. One sensitized to beef crystallin will not react to beef serum but will react to pork crystallin, chicken crystallin or even fish crystallin. This is organ specificity as contrasted with species specificity.

Like feathers and hair, the lens is derived embryologically from epithelium. All have undergone a process of denaturization, similar to that of the horny layer of skin. According to Krusius (1910) extracts of horse hoofs, cow horn, and human hair show similar organ specificity.

As Wells* states, "It is altogether reasonable that lens protein, keratin, mucin and other proteins whose function is not metabolism, should be non-specific. Each of these proteins has quite the same function to perform in every species, and is set off from the active tissues to perform it. There is no more reason why they should be species specific than any other functioning product of cell activity such as trypsin, epinephrine, thyroxin, insulin. They are all products of cell activity with a definite function and apparently alike in all species, just as lens proteins have been found to be." The logic of this reasoning also explains the frequently observed crossed sensitization to feathers from unrelated species of birds.

Eggs

Just as positive feather reactions and positive bird protein reactions do not necessarily correspond, one may be allergic to chicken egg without reacting to chicken meat. We have seen that this is true with other types of eggs such as shad.

Sensitization both to hen's egg and to chicken does occur and some authors have remarked on the frequency with which persons allergic to egg may also react to chicken and to fish.

Frequency. -Among the foods, egg is second only to wheat in allergenic frequency. It is of about the same relative importance as milk. Rowe observed that among 175 food allergies 57 were proved allergic to wheat, 35 to egg and 31 to milk. Eyermann found in 95 cases of nasal allergy that wheat was responsible for symptoms in 30, egg in 24, milk in 17. Vaughan observed positive skin reactions to wheat in 24 per cent, egg in 9.5 per cent and milk in 14 per cent.

Among children, especially those with eczema, egg allergy far exceeds milk and wheat allergy in importance. Hill found among 300 cases of infantile eczema that 131 reacted to egg as contrasted with 45 to milk and 35 to wheat. Hansel found positive egg reactions in 6.4 per cent of the adults and 10.9 per cent of the children with respiratory allergy. O'Keefe and Rackemann found 93 out of 125 children with allergic eczema sensitized to egg as contrasted with 46 to wheat and 32 to milk. I. C. Walker (1918) found that among 400 asthmatics 68 were food allergies. Of the latter, 25 gave positive reactions to wheat, 13 to egg.

While wheat may cause symptoms after ingestion, contact, or inhalation (flour dust), eggs have been shown responsible for trouble only following

*Wells, H. Gideon: *The Chemical Aspects of Immunity*, The Chemical Catalogue Co., New York, 1929.

contact or ingestion. It seems probable that if the opportunity for inhalation were greater, egg would cause symptoms in this manner also. This is a problem which merits study, the answer being available among those engaged in the manufacture of egg powder. Sutton mentions a patient so highly sensitized to egg that its presence in the room was sufficient to induce an attack. Here, conditioned reflexes may have played a part, if the patient saw the egg.

Early reports. The manifestations of egg allergy are sometimes most dramatic. This accounts in part for the fact that many of the earliest descriptions of food idiosyncrasy dealt with egg. LaRoche, Richet and St. Girons summarized these in their early monograph. Gelpke (1906) described a nine-year-old child who had abdominal pains, diarrhea and urticaria following the eating of egg and who, after a bath containing the whites of two eggs, developed a scarlatiniform eruption with edema of the face and difficult breathing.

Landmann (1908) studied a child of nine so highly allergic that an amount of egg the size of a pea resulted in angioneurotic edema of the tongue, vomiting, near collapse and a diarrhea which lasted for many hours.

Horwitz (1908) discussed the case of a man of 60 who had been allergic to egg since age 5. Even in old age symptoms were so severe as to include abdominal pain as severe as kidney or biliary colic, vomiting and diarrhea. Lesné (1911) described anaphylactic shock with near death from a few spoonfuls of egg taken by a child of eight. Schoffield (1906) studied a child of thirteen in whom the ingestion of egg caused urticaria, asthma and convulsions.

LaRoche, Richet and Saint Girons (1919) mentioned the case of Brazis, a woman who had always had constitutional reactions following the eating of egg. One day, after having avoided eggs as a food for years, she was opening an egg and inadvertently touched her eyelid with a finger. She promptly developed severe inflammation of the eyelid which lasted two hours. On another occasion she punctured both ends of an egg with a needle, as we do in blowing Easter eggs, and inadvertently pricked her finger at the same time. This promptly resulted in a "positive skin reaction."

It was but natural that only the most explosive cases should have been recognized early in the study of food idiosyncrasy. Even so, La Roche, Richet and Saint Girons discussed the less explosive cases under the heading *chronic alimentary anaphylaxis*. With the advent of the skin test in diagnosis, a method became available whereby mild sensitization, the etiology of which was often masked, could be identified.

The question of inheritance. There are a few cases on record in which egg sensitization appears to have been hereditary. They are the exception rather than the rule. The example most often quoted is that of La Roche who described milk and egg allergy in four generations of a family, the member of the first generation having been born in 1778.

Coca at one time suggested that it may be possible that one inherits not only the tendency to become sensitized and, probably, a predisposition to reaction on the part of certain of the shock organs, but also a predisposition to become sensitized to certain specific allergens. Although the majority of evidence today is rather against the last of these three possibilities, one cannot say that it is impossible. There is too much that as yet we do not know of the manner of inheritance of allergy. That the predisposition to sensiti-

tion is an hereditary factor is generally agreed. That certain shock tissues are hereditarily predisposed is not so immediately evident nor is it easy of experimental proof. However, it is a fact amply stressed by many of the earlier writers that conditions such as migraine, angioneurotic edema and the asthma-hay fever combination tend to run in families, these particular manifestations being repeated more frequently than the other allergic complexes involving different shock tissues. It is questionable whether the same conclusion would be reached today when with a clearer understanding of the process, the student of allergy usually finds on careful investigation that each patient has experienced symptoms attributable to more than one shock tissue. Nevertheless we can still state that migraine and inhalant allergy tend to run in families.

As to whether one can inherit an active sensitization to egg or ragweed, so many other factors may determine the final result that one cannot be certain. Granted a predisposition to egg sensitization, this might or might not become manifest during life, depending upon such factors as intensity and duration of exposure, opportunities for unusual gastrointestinal absorption, intercurrent illness, etc. From the clinical point of view these latter factors are the ones that can be controlled to some degree and are therefore the factors of greater importance. As a working hypothesis it seems better to assume that the tendency to sensitization is inherited and that the specific sensitization depends chiefly or entirely on nonhereditary factors.

It is in egg allergy especially that we find evidence suggesting the possibility of specific inheritance. The four generations of LaRoche are an example. Morell Mackenzie described a similar case. We should bear in mind that there may have been allergy to other foods as well as to egg and milk in the four generations. The fact that milk and egg are so frequently allergenic increases the probability of their having shown up in each of the four generations purely in accordance with the law of chance, without specific egg heredity. Furthermore, since egg allergy causes startling symptoms more often than many other foods, attention would be drawn to this rather than to other foods to which the individuals were also allergic.

Another factor which has suggested the inheritance of egg allergy has been the oft repeated observation that infants may develop symptoms on first exposure to contact with egg. There is no recognizable preliminary or sensitizing exposure in these cases. One might argue that the first exposure was an unrecognized one, the infant having come in contact with the substance without the knowledge of the parent; that the child may have been exposed to egg allergen in zwieback, later *appearing* to have symptoms when first eating egg itself. This is often the case; and careful questioning of the mother will often demonstrate that some food which she is certain caused symptoms on first exposure was actually ingested in some form at an earlier date. But in view of the careful investigations of a number of reliable men it would appear that this is not always so and that egg sometimes causes symptoms at its first ingestion.

Alternative explanation. Even so, it does not necessarily follow that egg sensitization represents a genetic inheritance. Ratner has shown that a fetus may become sensitized in utero to an allergen present in the maternal blood even though the mother is not allergic thereto. Donnally has demonstrated the passage of egg protein through the intestinal tract, the blood and the mammary gland into mother's milk, in a form still sufficiently like egg

allergen to be identifiable as such on skin testing. The child who reacts with symptoms following first egg exposure may have become actively sensitized while still in utero or at the breast.

There also exists the possibility of passive sensitization. Many times infants allergic to egg gradually lose this sensitization, and, as a rule, more rapidly than that to other foods. Stuart and Farnham state that it is the sensitization which is lost most quickly in childhood. However, children do not lose it as rapidly as does an animal passively sensitized at birth. In the latter it is a matter of four weeks or more while in the former it is often a matter of a similar number of months or years. Since the Prausnitz-Küstner reaction demonstrates that passive sensitization in human beings covers a period comparable to that in guinea pigs, prenatal human passive sensitization to egg as a factor of importance appears to be a most remote possibility.

Egg allergy in infants.—Hill found positive skin reactions in 59 per cent of 300 eczematous infants and young children. Egg showed by far the greatest frequency (131 cases).

“Egg sensitization was especially frequent in infancy and diminished with increasing age. Indeed many infants who had never had any known contact to egg were strongly allergic thereto. This raises the question as to the specificity of the reaction but since it was susceptible of passive transfer it appears to indicate a true atopy.” Hill says it is very common in young eczematous infants, to obtain positive tests to egg and to no other allergen. In older infants and in children, multiple sensitization is the rule. He quotes Moro as suggesting that sensitization to egg acquired in utero is often the starting point of allergy, that this does something to the individual which not only renders him allergic to egg but also makes him susceptible to other sensitizations as he comes into contact with other proteins. Egg white is said to be, of all proteins, the most difficult to digest. Walzer has found that incompletely digested egg protein circulates normally, postprandially, in the blood of some individuals. It is therefore conceivable that intrauterine sensitization may occur.

This is a potent point in the argument as to the possible fundamental difference between experimental anaphylaxis and clinical allergy. Those who believe there is a fundamental difference cite the observation that one may be naturally allergic to substances with which he has never been known to have come in contact. Egg allergy as described by Hill is an example. But the work of Ratner and others showing the possibility of intrauterine sensitization would explain this. Both sides of the argument are dealing primarily with concepts rather than facts. Neither can as yet muster sufficient incontrovertible evidence to prove the point.

Hill finds a distinct difference between milk sensitization and egg sensitization in infants. While some of the egg-sensitized infants do have symptoms from contact, many, even though positive by skin test, have never eaten egg and do not have symptoms when, later, they do so. A positive milk reaction, however, usually indicates that this food is actually causing trouble. “In practically all the infants who were positive to milk and to egg, it was possible to cure them by withdrawing cow’s milk alone and using a milk free diet.”

However, the writer does not recommend this as a routine procedure. As a routine a child reacting positively to milk and egg should have both eliminated from the diet, at any rate at the beginning. Indeed, I agree with

Rowe that egg allergy is such an important factor in young children that in the absence of positive reactions to egg and in the absence of improvement when the case is obviously one of food allergy, egg should also be eliminated as a trial procedure even though the skin reactions have been negative. Egg appears to cause cutaneous manifestations, either urticaria or eczema, more frequently than other symptoms.

Egg white and egg yolk. The question arises as to what portion of the egg should be used for skin testing. Schloss (1921) tested with egg albumin, egg globulin, ovomucin and ovomucoid. He found that all reacted positively although in some cases the two latter were positive while the former were negative. Tuft states that, of the various parts of the egg, sensitization is most usual to egg white or its component portions. He says that sensitization to egg yolk has been reported but that its actual existence is doubtful. Walzer states that it is doubtful that sensitivity to egg yolk occurs independently of allergy to egg white. He further states that testing with egg white is sufficient for the diagnosis of egg allergy and that separation into the constituent protein fractions is feasible but unnecessary.

This does not mean, as has been stated, that sensitization to egg yolk does not occur. I have often seen positive egg yolk reactions. Hill states that in eczematous children, reactions are often obtained to egg yolk and to egg white.

Symptoms.—Egg may cause any of the common allergic symptoms. It may produce anaphylactic shock. Vaughan and Pipes described the case of a young boy who inadvertently ate egg in mashed potatoes and was unconscious for four hours. Similar severe reactions are to be found in the literature. So far as I know there has been no death attributable to egg ingestion although Ratner (1928) described a suicide in an egg allergic following failure adequately to practice avoidance.

Possible sources of egg exposure.—

Almond cakes	Mousses
Almond paste	Muffins
Boiled salad dressing	Noodles*
Cotton and silk prints	Ovaltine
Cream sauces	Ovine (an egg powder)
Custards	Prepared beef juices
Dressed furs	Prune whip
Egg as such cooked in food	Sensitized photographic papers
Egg shampoo	Sherbets
French toast	Some baking powders
Glaced candies	Some prepared cake flours
Griddle cakes	Some prepared pancake flours
Hollandaise	Some preserved meat (forming an airtight casing)
Ice creams	Some sausages
Influenza vaccine and other virus or rickettsial vaccine grown on egg	Tanned skins and leathers
Macaroon	Waffles
Mayonnaise	Water color prints, "Tempera" found by Spain (1933) to cause eczema
Meringue	Whole wheat bread
Most cakes unless specially prepared	

*Plain noodles usually do not contain egg. Egg noodles may be made with fresh eggs or egg powder. Some noodle preparations contain corn starch or potato starch.

The list of possible sources of contact with egg sounds bizarre and is probably unnecessarily comprehensive. However, some very unusual responses have been reported. Duke describes persons who could eat rooster meat

but could not tolerate the amount of egg that contaminates hen meat. He describes a child who developed dermatitis of the face after having been kissed by parents who had eaten egg. Both Schofield and Coke have described symptoms following the eating of bread glazed with egg white. Schloss' early case experienced urticaria from contact with egg shells. Urbach and Joltrain have reported dermatitis from the handling of eggs. Rowe has described herpes progenitalis following egg ingestion. He mentions a woman who cannot eat food prepared in utensils in which eggs have previously been cooked and a man who experiences symptoms from the amount of egg in chocolate cream candy.

An egg allergic usually cannot eat the food, either cooked or raw, although very occasionally they may be tolerated when thoroughly cooked.

Virus and Rickettsial Vaccines.—These vaccines are grown on egg and, to date, the preparations made for clinical use have contained a minute amount of egg or chicken protein which, in rare instances, is sufficient to cause reaction. These reactions were found by Ratner and Untracht (1946) to be very seldom, and occur in those individuals who are very sensitive to egg or chicken, except for an occasional reaction which cannot be explained on that basis and which they think may be due to a toxic substance in the organism. They advise testing for evidence of sensitivity to the vaccine by using 0.02 ml. undiluted vaccine. They believe satisfactory results are obtained in the use of influenza vaccine by using doses of 0.1 ml. intracutaneously rather than the usually recommended dose of 1 ml. subcutaneously. Death has occurred (Rifkin, 1946) from administration of typhus vaccine to an egg-sensitive person.

Baking powder.—The following baking powders do not contain egg.

Royal
K-C
Calumet

Ice cream.—Egg is used in some ice creams but most commercial ice creams do not contain it.

Species and group specificity.—The question whether one who is allergic to hen's egg may substitute other eggs such as duck, goose, or guinea requires further study.

Welsh and Chapman (1910) found a common antigen in all avian eggs. At the same time each species had its own specific antigen, different from those of other species. This is similar to the situation in the equine family, and in the cereal grains.

Wells has found (1911) five chemically distinct antigens in hen's eggs, corresponding to five chemically distinct proteins. One or more of these is species specific while the rest are group specific. Crystallized duck egg albumin and crystallized hen egg albumin appeared to be identical or practically so, both chemically and allergenically. Only one of the chicken egg proteins, conalbumin, is identical with the albumin in chicken serum.

If these early anaphylactic experiments of Wells, Hektoen and Cole and of Dale and Hartley apply directly to clinical allergy we may say that if a person is allergic to the conalbumin of egg he will react positively both to egg and to chicken: if one is allergic to crystallized hen's egg albumin he will not be able to eat duck eggs or any other type of avian egg: if one is allergic only to one of the hen's egg specific fractions, he will not be able to eat hen's eggs but will be able to eat chicken and other varieties of avian eggs. If a

person allergic to hen's eggs wishes to try other varieties, the attempt is justifiable but should preferably be preceded by testing for sensitization thereto.

According to Lewis and Wells ovomucoids from the eggs of birds of different species show some immunologic crossed relationship although they can be distinguished by refined methods. Similar conclusions were reached by Emmerich with the egg yolk protein of hens, fish and turtle. Dunbar (1910) found no evidence of crossed anaphylactic reactivity between the blood of certain fish and the roe of the same fish. He did find crossed reactivity between the roe of fresh-water fish and that of salt-water fish.

Burchard (1934) found crossed allergenic activity among all of the species of common barnyard fowl, but very little in parrot and none in dove eggs. There is need for more clinical investigation of crossed sensitization to the eggs of different species.

MAMMALIAN FOODS

The list of mammals used for food is a long one even if we include only the staple foods of such remotely separated peoples as Eskimos, African natives and Cannibals of the South Sea Islands. Even among civilized communities there is great variation. Thus the guinea pig or cavy which in this country and Europe is usually seen only in the laboratory, is a popular food in South America. For routine allergic studies, the chief foods are beef, veal, lamb, mutton, pork and several varieties of game food. In Europe horse meat must also be considered. Among the Eskimos and Chinese, dog meat is an occasional food. The familiar chow dog has been raised in China for centuries as a source of food supply and gives justification to the familiar army phrase for food.

Group sensitization.—As with birds, we find immunologic evidence of crossed sensitization among closely related mammals. Experimentally, antibodies are not produced against an animal of the same species as that being used for antibody production. The same is true to a degree with closely related species. Thus antibodies are not obtained following injection with the blood of wolves or foxes into dogs or following the injection of horses with donkey blood. The wider the divergence of the species, the less evidence is there of crossed immunologic relationship. Thus Wells sensitized animals against human blood. This antihuman serum showed 100 per cent precipitin titer when mixed with human blood or with the blood of anthropoid apes. Against common monkey blood the titer was but 92 per cent. Against capuchins and spider monkeys it was 78 per cent. Against marmosets it was 50 per cent and was further reduced to zero against lemurs.

Horse meat.—Richet has described a man who had served in the French cavalry during the World War and who ten years later ate horse meat for the first time. This was immediately followed by asthma with urticaria and albuminuria. He had never had these symptoms before. He has eaten no horse meat since and has had no recurrence.*

Horse meat is used as a food among the poorer classes in parts of Europe. In parts of Russia, mare's milk is fed to infants.

Kolle and Hetsch state that Tartar children reared on mare's milk are very reactive to horse serum injections, that children nourished exclusively on horse

*Richet, Charles, Paris. Personal communication.

flesh show more immediate reactions from horse serum injections than others, and that in Holland where horse flesh is rather widely eaten, asthmatics often give positive horse allergen reactions.

Beef—Veal.—Vaughan found positive skin reactions to beef in 2 per cent, Rowe in 2 per cent, Hansel in 6.4 per cent with intracutaneous testing and 1.8 per cent by scratch. Rowe found beef responsible for symptoms in 2 per cent, Eyermann in 6 per cent. I feel that it would be a safe average to say that about 4 per cent of food allergies are allergic to beef.

Theoretically there should be no allergenic difference between beef and veal. That there may be some difference, especially with very young veal, is suggested by Kern's case.* Veal is popularly considered undesirable as a food if slaughtered younger than age four weeks. Such very young veal is termed monkey veal or bob veal. It has been shown that as a food it is as wholesome as older veal. However Kern's patient would invariably develop migraine after eating monkey veal but not after older veal.

Beef and veal are usually recognizable as such and can be easily avoided, although in stews, broths, soups and in veal used as a substitute in chicken salad they are sometimes hard to recognize or avoid. The question has been raised whether parenchymatous tissues such as liver, sweetbreads, brains, kidney must be avoided as well as muscle meat. Unless clinical trial in the individual case indicates otherwise, all should be avoided.

Nearly all canned soups contain some beef broth. This applies not only to vegetable soups but to other meat soups, such as chicken.

Jell-O may contain pork gelatin or beef gelatin or both. Knox Gelatin is made from beef. A pork allergic found that he could eat Knox Gelatin without symptoms but could not eat Jell-O.

The following description of a child allergic to beef gelatin is so interesting that I quote verbatim from the mother's report. "The child vomited almost at once on eating eggs (he did so the second time) then began to have croup and at three he screamed several hours and had bladder disturbance after eating boiled custard. Now we are very careful even about ice cream. He got very irritable on hot cakes and rubbed his eyelids so that I investigated the baking powder and there was dried egg in it. The Royal Baking Powder seems to be made from grapes but he gets bleary eyed on drinking grape juice. So there you are! He walked the floor frantically holding one ear several times after eating figs, saying his ear had 'shut up.' I sent for the doctor and his ears had swollen shut. He ate gelatin and his gums swelled like Vincent's angina, and he was very sick for a week. He had ulcers on his tonsils and bronchitis with high temperature. So, I have been surprised to see not much warning about gelatin. He used to clear his throat almost constantly and had dreadful itching about the rectum. He recovered when off of peaches, apricots and apples."

Lamb—Mutton. Rowe, likewise Vaughan, found lamb allergenic in 2 per cent. Hansel found it positive in 5.9 per cent when tested intracutaneously, in 3.6 per cent cutaneously. Eyermann did not find lamb a cause of trouble in his 95 cases. Of the three common mammalian meats, beef, lamb and pork, this is less frequently allergenic than the others and has therefore been used by Rowe in his elimination diets and by Vaughan in the trial diets.

Pork—Ham—Bacon. Pork is generally conceded the most frequently allergenic of the three mammalian foods under discussion, varying in frequency in the listings by Eyermann, Rowe, Vaughan, and Hansel from 1.2 per cent to 5.9 per cent.

Pork, ham and bacon can scarcely be considered the same food. Even different ham preparations vary in their allergenic activity. The manner of feed-

*Kern, Richard A.: Personal communication.

ing the hog such as "peanut fed," "corn fed," and the method of curing and spicing or seasoning probably play a part. I have seen persons who could not eat fresh pork but could eat ham or bacon. Others cannot eat ham but will tolerate pork and bacon. Bacon appears to cause symptoms less frequently than either ham or pork. Others have symptoms from all three.

Pork, ham and bacon can usually be recognized as such in the food. Persons highly sensitized to this allergen may be unable to eat food which has been prepared in pork lard or hog lard or foods such as pies or cakes in which it has been used as shortening. Fortunately the prepared vegetable lards or butter may be substituted provided the individual is not allergic to them.

Garcin observed a man with attacks of diarrhea and accompanying eosinophilia of 80 per cent, due to pork allergy. Differentiation from trichinosis presented a problem, early in the study of the case.*

MILK AND MILK PRODUCTS

Various proteins. -Wells and Osborn (1921) found that milk contains four proteins which are chemically and immunologically distinct. These are casein, lactalbumin, lactoglobulin and an alcohol-soluble protein. Milk globulin and serum globulin are chemically indistinguishable. Lactoglobulin sensitizes to beef serum and vice versa. Therefore it is not surprising that occasionally milk allergies are also beef allergic. Lactalbumin and serum albumin are however distinct proteins. Lactalbumin appears to be more species specific. Casein is much less so. One sensitized to the casein of cow's milk will probably also react to that of goat's milk or sheep's milk or ass's milk. Fortunately, sensitization is usually to the lactalbumin fraction and the milk allergic may therefore often tolerate goat's milk or other available milk. Ass's milk has been used for this purpose in Europe.

As stated by Wells† "casein from the milk of an animal of any given species shows a closer biologic relationship to the casein of another species than it does to either the whey proteins or to the serum protein of its own species; the same is true of the chemical relation."

Frequency. Milk allergy is of about equal frequency with that to egg. Eyermann found it responsible for nasal symptoms in approximately 15 per cent. Rowe found it of allergenic importance in 31 per cent of food allergies. Vaughan found positive skin reactions in 14 per cent. Hansel observed positive endermal reactions in 13 per cent, positive dermal in 11 per cent. Peshkin found positive skin reactions in 10 per cent of atopic children. Balyeat reported 47 per cent positive milk reactions in atopic eczema. O'Keefe and Rackemann in 26 per cent. Rowe found 5.5 per cent of 234 asthmatics allergic to milk.

In replies to a query from the Bureau of Health and Public Instruction of the American Medical Association, Cooke estimated the incidence of milk sensitization in all children as about 0.3 or 0.4 per cent; Rackemann as less than one per thousand; Waldbott as 3 to 5 per cent; and Rowe as between 2 and 7 per cent. Vaughan estimated the frequency of milk allergy in a normal population (adults and children) as from 1 to 1.5 per cent. Alexander reported the incidence of milk intolerance in a large gastrointestinal clinic including adults and older children as 5 per cent.

*Garcin, Ramon D., Jr., Brooklyn. Personal communication.

†Wells, H. Gideon: *The Chemical Aspects of Immunity*, ed. 2, The Chemical Catalog Co., New York, 1929.

Like egg, milk affects children more often than adults and again like egg, milk sensitization tends to disappear with advancing years. Like egg, this food can produce practically any allergic manifestation including shock. Such instances were recorded early in the annals of food idiosyncrasy.

Probably with no other food has sensitization been produced as often by overfeeding. It seems probable that much milk allergy among children results from parental forcing.

A woman in the writer's experience, allergic to milk, dated the onset of her allergic dermatitis from an intramuscular injection of Lactogen. Bernstein and Ginsberg (1937) have observed an asthmatic treated with injections of a fat-free milk preparation who became sensitized thereto, with consequent asthma and shock. They found it possible to sensitize guinea pigs to these same commercial milk preparations.

Sensitization to other allergens contained in milk. Some apparent sensitization to milk is actually due to some other allergen that has passed through into the milk. Donnally (1930) has reported the presence of egg allergen in mother's milk. Thommen (1922) has demonstrated that ragweed allergen may pass into milk and cause symptoms. Bowman and Walzer have called attention to the possibility of flaxseed allergen in the milk of cows fed on flaxseed meal. Balyeat has reported symptoms in a wheat allergic following the taking of milk from cows fed on bran. Black has demonstrated that peanut allergen may pass into the milk. Reported sensitization to human breast milk was in all probability actually sensitization to some food allergen absorbed and excreted in the milk.

Degree of sensitization. There are all grades of reactivity to this food, from those who experience severe symptoms after the ingestion of one drop of diluted milk, to those who find that they can ingest it with impunity on occasion but will get into difficulties after taking it for several days in succession. There are some who cannot tolerate fresh milk but, being mildly atopic, can take boiled milk, milk cooked in the food, or canned, condensed or dried milk.

Recognizing that certain persons reactive to raw or pasteurized milk can tolerate milk modified by heat, Ratner and Gruehl concluded from investigation that loss in antigenic properties in heated milk is due to coagulation of the whey protein. Furthermore heating facilitates digestion, diminishing in a measure the absorption of native protein into the blood.

"Evaporated milk" is, as the name implies, ordinary milk evaporated down to about half its volume and sterilized. "Condensed milk" is whole or skimmed milk evaporated to about half of its volume, to which sugar is added as a preservative. It is not sterilized. "Filled milk" is skimmed milk to which cocoanut oil has been added in place of its natural cream. "Malted milk" contains malted barley, wheat flour, and milk.

Cream—Butter.—I have seen children who could tolerate lactic acid milk or buttermilk but not fresh milk. Others can take heavy cream or butter. Some are so highly allergic that they cannot tolerate the small amount of allergen in butter. Rowe has described the case of a woman who, allergic to milk, "has picket fence staggers, weakness and trembling in the arms and legs when she takes butter." She can tolerate cream in her coffee for two days but after continuing with it for 48 hours develops symptoms.

Duke, likewise Vaughan and Pipes, have reported severe reactions in milk allergies who have been transfused from donors who had recently taken milk.

Human milk.—Duke reports the case of a woman with eczema “allergic to milk from her own breast.” Some milk persisted after weaning. She was treated with autogenous milk dilutions. The breast secretion ceased and her eczema cleared up.

Milk allergy in animals.—Allergy to milk has been described in animals. This is especially true in dogs who at times have eczema therefrom. Schroeder described eczema and conjunctival, nasal and gastrointestinal symptoms in a young walrus, associated with milk allergy.

Possible contact sources.

Aunt Jemima's Pancake Flour	John Bull Food
Blanc mange	Kefir
Blood transfusion	Koumiss
Bread as usually prepared	Leben
Cake	Macaroni
Canned fish balls	Malted Milk
Carnrick's Soluble Food	Milk chocolate
Cookies	Nestlé's Food
Cream Sauce	Noodles
Custards	Oleomargarine (usually contains
Dryco	40% cream)
Fritters	Peter Pan Bread
Ice cream	Spaghetti
	Steinhardt's Infortina

Milk substitutes.—Except possibly in some cases where infant feeding is a problem, milk substitutes are rarely required. Except for calcium all of the constituents may be adequately supplanted by other natural foods. When milk is prohibited, it is a safe procedure to supplement the diet with calcium in some form. Inorganic calcium appears to be as efficacious as organic. Powdered calcium gluconate, one or two teaspoonfuls morning and evening, suffices.

With infants who must avoid cow's milk, human milk should be substituted if possible. Bottled human milk is now becoming available.

Goat's milk.—A satisfactory canned goat milk may be obtained from Meyenberg Milk Products Company, Salinas, California, distributed by Goat Milk Products Company, Los Angeles, California. The patient should be tested with this milk prior to its prescription. Fresh goat's milk should be prescribed only from sources certified free from brucellosis.

Soy products.—Sobee (Mead Johnson & Company, Evansville, Indiana) may be purchased at all drug stores. Its composition is as follows:

Soybean flour
Olive oil
Arrowroot starch
Dextri-maltose
Dicalcium acid phosphate
Sodium chloride

Mull-Soy (The Muller Laboratories, Baltimore, Maryland) is a vegetable milk substitute. Its composition is as follows:

Soybean
Dextrose
Sucrose
Soybean oil
Minerals
Vitamins A and D (fish liver oil)

Allerteen is prepared by the American Dietetics Company, Yonkers, and contains soy flour, cocoanut, cane sugar, hydrogenated soy oil, potato starch, dicalcium phosphate, salt, lecithin and maple flavor.

Nutramigen is a product of Mead Johnson and Company, Evansville, and contains only amino acids and polypeptides plus dextromaltose, olive oil, arrow-root starch, brewer's yeast, calcium gluconate and mineral salts.

Synthetic infant food.—In view of the fact that children are so often allergic to milk, egg or the cereal grains, Cohen and collaborators have developed a substitute food containing approximately the same composition, including vitamins, as milk. This consists of beef, cauliflower, tomatoes, carrots, spinach, cane sugar, olive oil, codliver oil, gelatin, calcium lactate, acid sodium phosphate and water. Its food value is 19 calories per ounce. Beef provides the growth promoting vitamins and the antipellagra factor. Calcium is derived principally from carrots and cauliflower; iron and vitamins from spinach, and vitamin C and flavor from tomatoes. Cane sugar and olive oil bring the carbohydrate and fat content to approximately that of human milk. Gelatin is used to emulsify the fat. The inorganic salts are added to bring the total calcium to one gram and phosphorus to 1.5 grams per quart of formula.*

The authors report good results from treatment except in one case found allergic to one of the constituents of the formula. "With substitution of turnips for spinach in the formula, good results were obtained."

Rowe (1931) published a formula containing strained homogenized meat—lamb or beef—no vegetables, a choice of tapioca or potato flour and sesame or soy oil. Stuart (1945) has described a satisfactory method for preparing this formula in the home.

Cheese.—Casein is a protein allergenically common to milk from various species. Since it is the chief constituent of cheese, one might be justified in assuming that in the presence of sensitization to cow's milk, one should avoid all varieties of cheese. However it should be borne in mind that lactalbumin sensitization or sensitization to the whey fraction is more frequent than that to casein or the curd fraction. Therefore, milk allergies may tolerate cheese. Sometimes whey is present but usually not more than in butter. Some cheeses are made of whey or contain large amounts and should be avoided by milk allergies. These include the milk cheeses such as cottage cheese, cream cheese, Neufchatel, Gervais, buttermilk cheese, the Scandinavian or Danish myost.

The following cheeses are made from cow's milk.

American Cheese	D'Isigny	Koesher Gouda	Pennsylvania Pot
Appetitost	Dunlop	Leyden	Provolone
Bondost	Edam	Liederkrantz	Rabbit
Brick	Emmenthaler	Limburger	Rat
Brie	English Dairy	Lodigiano	Sage
Buttermilk	Floedoest	Munster	Sap Sago
Caciocavallo	Gammelost	Myost	Sbrinz
California Jack	Gervais	Neufchatel	Smearcase (Schmier-
Camembert	Gorgonzola	Oka	kase)
Cheddar	Gouda	Parmesan	Sorrento
Cheshire	Goya	Pineapple	Stilton
Cottage	Gruyere	Pont L'Eveque	Store
Cream	Hand	Port du Salut	Schweizer
			Swiss

Goat's milk cheeses.—The best known is Gjedeost, a sweet, rich, strong-flavored, brown Norwegian milk cheese, moist but firm enough to slice well.

*This preparation is made by Mead Johnson & Company under the trade name Cemac.

Gorgonzola is sometimes made from goat's milk, sometimes from cow's milk. Lipton's is made from goat's milk, seasoned with pepper and spices. Montasio is sometimes made from goat's milk, sometimes from cow's milk.

Sheep's milk cheese.—Roquefort is the most famous. Next is Romano. Other similar Italian sheep's milk cheeses are Sardegna, Toscano and Pecorino. The latter are grouped as Romano cheeses and there are numerous imitations made from cow's milk. Therefore one must be certain of obtaining the original if one prefers a sheep's milk cheese.

Buffalo milk.—Latticini is made from tame buffalo milk.

Other cheese ingredients.—The ingredient most often thought of is a mold. In the preparation of nearly all cheeses preliminary fermentative activity is accomplished with the lactic acid bacillus. Following this, in certain cheeses molds play an important ripening function. This is especially true in Roquefort and Camembert but more particularly in Gammelost in which the fungus practically replaces the curd, as a consequence of which one is no longer eating cheese flavored with fungus but rather, fungus flavored with cheese.

Some cheeses contain added ingredients which may be allergenic. Examples are the penicillia of Camembert and Roquefort; pimento in various pimento cheeses; sage leaves or corn juice and spinach leaves in Sago cheese; coumarin or blue melilot in Sap Sago cheese; cloves and caraway seeds in Leyden cheese; and caraway seeds or various herbs in Hand cheese.

CHAPTER XXXIX

MISCELLANEOUS INFORMATION FOR FOOD ALLERGICS

A number of questions are raised by the person with food allergy, the answers to which are at times difficult. One of the first questions after the patient has listened to a long list of foods which must be avoided is often, "But, Doctor, what *may* I eat?" There are times when the "don't eat" list sounds completely prohibitive. Invariably, however, there are many additional foods which may be included as substitutes. The patient's dismay may often be relieved by providing him with a list of foods commonly used, on which prohibited foods are crossed off. The remaining list is usually surprisingly long. The list on page 144 may be used for this purpose.

Another difficulty encountered by the patient may be that, given a reasonably large variety of available foods, he does not know how to combine them into tasty dishes. There was a time when home cooking was considered an art and the domestic person knew how to make all sorts of foods into palatable mixtures. Today bread is rarely cooked in the home, canned vegetables are preferred to the fresh, ice creams and many desserts are purchased ready-made and homemade soups are almost unknown. Much of the difficulty in preparing palatable substitute foods is due to lack of imagination or versatility and, shall we say, laziness on the part of the cook. Even those who must avoid wheat, egg or milk or a combination of all three, will find palatable substitute recipes in any good standard cook book. The atrophy of epicurean and culinary inventiveness has reached such a stage that today the best recipes are often found in the advertising matter of corporations which desire to increase the sales of their special products. The Fruit Dispatch Company,* for example, has a booklet with recipes containing banana. The Royal Baking Powder Cook Book, first published in 1878, is still available for householders, listing as good recipes as may be found in standard cook books. The W. K. Kellogg Company furnishes for the asking wheat-egg-free recipes and wheat-free recipes from which the consumer may make dishes using the Kellogg products as a base. For greater convenience the recipes are printed on card index cards.

Even so, many will not avail themselves of these suggestions and will continue to complain that the dietary proscription prevents the preparation of palatable meals. Since it is difficult indeed to change the trends of the time, since housewives will continue to purchase ready-prepared foods, and since many of us find it necessary to eat in restaurants where one has no voice in the preparation of food, it becomes important to know so far as possible the constituents of widely used and nationally advertised food preparations and mixtures. Most of these are proprietary. Many of the more outstanding manufacturing concerns realize the importance in allergy of knowing constituents and give information without hesitation. With other products, information may at times be obtained concerning constituents which they do not contain although those which they do contain are kept secret. The knowledge acquired by correspondence is necessarily miscellaneous.

*Pier 3, North River, New York.

Foods and Dishes Concerning Which Question Is Often Raised as to Ingredients*

Allison Flour. Cottonseed.

Aunt Jemima's Pancake Flour. Wheat, corn, rice, rye flour, sugar, milk, salt, baking powder.

Aunt Jemima's Buckwheat Flour. Corn, wheat and buckwheat.

Baking Powder. This is a substitute for yeast and acts through liberation of carbon dioxide from the combination of acid with alkali. The alkali is usually sodium bicarbonate. Phosphate baking powders have some form of phosphoric acid as the acid constituent; alum powders have aluminum sulfate; tartrate powder contains cream of tartar or tartaric acid. Cornstarch is the customary filler in all baking powders. Filler is required to prevent absorption of moisture and consequent premature combination of acid and alkali.

Some baking powders contain egg powder. The following brands do not contain egg. K.C.; Royal (contains cornstarch, cream of tartar, tartaric acid, and sodium bicarbonate); Calumet (contains cornstarch, sodium bicarbonate, sodium aluminum sulfate, calcium acid phosphate).

Beef Juices (Puro). Meat juice, egg white.

Beer (ale, stout, porter). Fermented malted grain, usually barley; wheat, rye, oats, rice and corn may be used. Hops (dried flower of the hop vine) are usually added.

Bemax. Contains rye, barley and wheat germ.

Berger's Food. Wheat flour and pancreatic extract.

Blanc Mange. Gelatin, Irish moss and milk. Cornstarch, ground rice and arrowroot are often substituted.

Bologna. Beef, veal, pork and spices.

Borden's Malted Milk. Barley malt, wheat flour, whole milk.

Brandy. Distilled from fermented juices of grapes. It may be made from peaches, cherries, apples and other fruits.

Brittle Bits. Malted wheat and barley.

Buckwheat Bread. Buckwheat meal, wheat, yeast and salt.

Buckwheat Flour. Used on bottom of many breads to prevent burning.

California Wheatine. Wheat.

Canned Tomato Soup. Tomato, butter, onion, sugar, salt, flour, spices.

Carnrick's Soluble Food. Malted wheat, dried milk, milk sugar.

Catchup or Catsup. Originally a sauce of spiced mushrooms. Various catsups are made differently but are likely to contain tomatoes, onions, spices, vinegar, sugar, green walnuts and a thick purée of oysters or other shellfish.

California Health Food Service (1926 Telegraph Ave., Oakland, California) lists 52 bakery and confectionery products for use in wheat, egg, milk and cottonseed substitute diets.

Cellu Dietetic Products (Chicago Dietetic Supply House, 1750 West Van Buren Street, Chicago). "Cellu juice pak fruits" are packed in their own juice without added water or sweetening. Cellu vegetables are canned in water without addition of salt or sugar. Cellu fruit juices "have not been diluted or sweetened but are packed just as they are pressed from the fresh fruit." Cellu flours: see wheat substitute flours.

Cerealine Flakes. Corn.

Chewing Gum. Originally spruce gum. Later paraffin wax variously flavored. Now chicle is almost universally the chief ingredient. Chicle is a gum derived from the latex of the *Achras sapota* or sapodilla tree. The fruit of the tree is one of the most delicious tropical fruits. (See list of exotic foods above.)

Chop Suey. The ingredients vary in different establishments but are likely to contain chicken, fish or other meat, bamboo shoots, bean sprouts, especially soy beans, mushrooms, rice, noodles and ginger.

Chow Chow. A mixture of pickled vegetables with mustard.

Chutney. An East Indian pickle generally containing mangoes, raisins, tamarinds, lime, ginger, chilis and other spices. Domestic chutneys usually consist of some sweet fruit as designated, with acid flavor added from lemon, tamarinds, etc., and seasoned with chilis, etc.

Citrus Concentrates. Pure concentrated fruit juices with nothing added and nothing extracted except water. (Citrus Concentrates, Incorporated, Dunedin, Florida.)

*Acknowledgment is made to Tuft, Louis: Clinical Allergy (Saunders, 1937), for a list of these notations.

Clapp's Wheatheart Soup. Wheat germ, vegetable, cereals.

Coca-Cola. Caffeine, caramel, essential oils (cinnamon, coriander, lemon, neroli, nutmeg, sweet orange), glycerin, lime juice, phosphoric acid, soluble extracts of coca leaves or kola nuts, and water (carbonated).

Cocomalt. Sucrose, skimmed milk, selected cocoa, barley malt, flavoring, irradiated viosterol.

Cooking Oil. Cottonseed oil.

Corn Flakes. Corn, malt extract, sugar, salt.

Cottolene. Cottonseed oil and beef suet.

Cream of Wheat. Entirely wheat.

Cream Sauce. White sauce and eggs.

Crisco. Cottonseed oil.

Curry. A highly seasoned East Indian condiment usually containing turmeric, coriander, black pepper, cayenne pepper, some fenugreek seed, cumin, ginger and lime.

Custard. Egg, milk, sugar, flavoring.

Diastased Farina. Malted cereal food.

Dormi. (The Battle Creek Food Company.) Malt, cocoa, vanilla, lactose, salt.

Dried Beef. Beef, pickled in salt, sugar or molasses with saltpeter added, then smoked like a ham.

Dryco. Irradiated milk. **Special Dryco** also contains rice "polish."

Falona. Wheat, oats, barley and bean flour.

Farina. Wheat.

Fish Balls. Fresh haddock, potato flour, milk, spices.

Fluffo. (Procter and Gamble, Cincinnati.) Does not contain peanut oil.

Force. Malted wheat and barley.

Frankfurters. Beef, pork and spices stuffed in sheep casings.

French Dressing. Olive oil, vinegar, salt, pepper, spices.

Fritters. Flour, baking powder, egg, milk.

F. S. Granulated Hominy. Corn.

Gelatin. Usually made from beef, veal or pork. Knox Gelatin is said to be from beef, Jell-O from beef and pork. Cattle, sheep, goat, pig and fish hides and connective tissues may be used.

Genesee Dessert Powder. Butterscotch (granulated sugar, cornstarch, brown sugar, flavoring, salt, U. S. certified color). Vanilla (granulated sugar, cornstarch, flavoring, salt, U. S. certified color). Chocolate (granulated sugar, cornstarch, powdered skim and whole milk, cocoa, flavoring, salt).

Gin. As made today this is distilled or rectified spirit from wheat, barley, malt, rye or corn to which certain extracts are added. These may include: almond meal, angelica root, angelica seed, aniseed, calamus root, caraway seed, cardamom seed, cassia (cinnamon), cloves, coriander seed, fennel seed, grains of paradise (cardamom), juniper berries, lemon peel, licorice root, nutmeg, orange peel, sweet orange, neroli (extractive of orange blossom), orris root, sloe berries, turpentine, singly or in any combination. All except angelica, calamus, fennel, juniper and sloe have been listed as being allergenic.

Ginger Ale. Carbonated beverage made from ginger (or ginger extract), lemon juice (or lemon oil and citric acid). Capsicum extract is frequently substituted in part for ginger.

Goat Milk. The Meyenberg product contains only evaporated goat milk.

Grape Nuts. Wheat, malt, barley, salt, yeast.

Grape Nuts Flakes. Wheat, malt, barley, salt, yeast.

Goose Liver. Calf's liver, pork, goose liver.

Hausbrot or Tafelbrot. Wheat and rye.

Hecker's Hominy. Corn.

Hecker's Superlative Self-Raising Flour. Wheat, phosphate or soda, salt.

Heinz Products. (H. J. Heinz Company.) The following contain no wheat, egg or milk.

Apple Butter

Baked Beans

Beef Broth

Chili Sauce

Chow Chow

Gumbo Creoles

Jellies

Mince Meat

Mustard

Mustard Sauce

Olives

Olive Oil

Onion

Peanut Butter

Pepper Pot Soup

Preserves

Rice Flakes

Salad Cream

Sour Pickles

Sweet Mustard Pickles

Sweet Pickles

Tomato Catsup

Tomato Juice

Turtle Soup

The following soups contain milk but no wheat or egg.

Asparagus	Mushroom
Bean	Oyster
Celery	Peas
Corn Chowder	Spinach
Cream Soups	Tomato

The following contain egg but no wheat or milk.

Consomme
India Relish
Mayonnaise Salad Dressing
Sandwich Spread

The following contain wheat but no egg or milk.

Clam Chowder
Mock Turtle Soup
Vegetable Soup

The following contain wheat and egg but no milk.

Mock Turtle Soup
Noodle Soup

The following contain milk and wheat but no egg.

Macaroni in Cream Sauce
Scotch Broth
Spaghetti in Tomato Sauce

The following contain wheat, egg and milk.

Date Pudding
Fig Pudding
Plum Pudding

Hollandaise. Eggs, butter, lemon juice.

Honey. There have been many undoubted cases of allergy to honey. It is conceivable that this is due to sensitization to the plant from which the honey is obtained, that is, to the nectar, or to the pollen of the plant or of other plants carried into the honeycomb by the bees; or to allergy to bee itself. Severe allergic reactions, even fatalities have followed the sting of a single bee. There are many kinds of honey depending upon the plant source, such as clover, alfalfa, buckwheat, mountain sage, chinkapin, heather (in Scotland), orange, mesquite, catclaw. The fame of the particular honey rests in great measure upon its source. The famous Grecian honey is from wild thyme, the Scotch from heather, while in this country clover and alfalfa honeys are well thought of.

Ratner and Gruehl demonstrated that those who cannot tolerate honey may be allergic to the specific protein element of the nectar from which it is derived, such as buckwheat.

Horlamus "All Rye Bread." (Mrs. I. Horlamus, Riverside Station, Box 1712, Miami, Florida.) Contains pure rye flour, Fleischmann's yeast, brown sugar, salt, water and Crisco. When cottonseed is to be avoided lard is substituted, on order, for Crisco. Does not contain egg, milk, wheat or oatmeal. It is available in vacuum-sealed tins. We have found this "canned bread" still fresh after 8 months in the tin. It may therefore be ordered in quantity. Horlamus cookies may also be obtained, made from pure rye flour, brown sugar, Crisco, vanilla, and nutmeg or cinnamon. Pecans may be added if desired.

Horlick's Malted Milk. Barley, wheat flour, desiccated milk, malt, NaHCO_3 .

H. O. Co. Buckwheat Pancake Flour. Cornmeal, buckwheat, wheat.

H. O. Co. New Process Hominy. Corn.

Huskies. Wheat, sugar, salt, flavoring.

Ice Cream. Egg, milk and flavors.

Ices. Fruit, egg, flavoring.

Jam. A sweet preserve. If the rind of the preserved fruit is included it is customarily called marmalade. The best jams contain none other than the specified fruits, sugar and water. Cheap jams usually also contain apple juice, or corn syrup or both.

Jell-O. Jell-O is usually made from beef gelatin. Occasionally pork gelatin is also added.

Contains cane sugar, gelatin, pure fruit flavors, U. S. certified colors for all flavors except lemon which is vegetable color. Added fruit acid from grapes and lemons (tartaric and citric acids).

D-Zerta. "Lemon, orange, strawberry, raspberry, cherry, lime" contain saccharin, gelatin, citric acid, fruit flavors, U. S. certified colors.

Jell-O Ice Cream Powder. "Vanilla, strawberry, lemon, maple" contain sugar, Karaya gum, salt, flavoring, U. S. certified colors.

"Chocolate" contains sugar, Karaya gum, cocoa, salt, vegetable color.

"Unflavored" contains sugar, Karaya gum, salt.

Jell-O Freezing Mix. "Strawberry" contains sugar syrup, tapioca flour, strawberries, salt, U. S. certified color.

"Chocolate" contains sugar syrup, carob bean flour, gelatin, cocoa, salt, U. S. certified color.

"Maple Walnut" contains sugar syrup, carob bean flour, maple flavor, walnuts, salt, U. S. certified color.

"Orange Pineapple" contains sugar syrup, carob bean flour, gelatin, true fruit (orange, pineapple), salt, U. S. certified color.

"Vanilla" contains sugar syrup, carob bean flour, gelatin, vanilla extract, salt, U. S. certified color.

"Tutti-frutti" contains sugar syrup, carob bean flour, gelatin, true fruit (pineapple juice, maraschino juice, cherries, red and green), salt, U. S. certified color.

Jelly. Although any fruit can be used in jam or preserves, only those which contain sufficient pectin may be made into jelly. Jellies flavored with fruits low in pectin usually have the latter added as a base. Apple pectin is usually used. Commercial mint, raspberry, strawberry, pineapple, and grape jellies usually contain apple pectin.

John Bull Foods. Dried milk and malted cereals.

Junket. Milk, rennet, vanilla, cinnamon or nutmeg.

Karo Syrup. Corn syrup.

Kefir. Fermented cow's or goat's milk.

Knupfel. Rye and wheat.

Kommisbrot. Rye.

Koumiss. Fermented milk of mares or asses, also from cow's milk fermented by yeast.

Kremel. Cornstarch, dextrose, sucrose.

Leben. Cow's milk fermented by special coagulant.

Lima Rice Flakes. (Battle Creek Food Company.) Yeast extract, rice, lima bean, salt.

Liqueurs. Sweet liquors are made by distilling and mixing various alcohols with essential oils, flavors and syrups.

Liver Sausage. Pork, onions, pistachio.

Log Cabin Syrup. Granulated sugar, maple sugar.

Macaroni. Wheat and milk.

Macaroons. Almond meal, cocoanut, eggwhite and sugar.

Maltine. Malted barley, wheat, oats, vitamins B and C.

Malt-O-Meal. Farina, toasted malt barley.

Marinated Herring. Packed in white vinegar.

Matzoth. Wheat flour and water.

Mayonnaise. Olive or vegetable oil, eggs, vinegar, spices.

Mazuma. Corn.

Mead's Vitamin Products. (Mead Johnson & Co., Evansville, Indiana.) Oleum percomorphum consists of a blend of the liver oils from percomorph fishes and cod-liver oil. Compound syrup oleum percomorphum is the same oil with added olive oil in malt syrup. Cod-liver oil fortified with percomorph liver oil contains 95 per cent of the former and 5 per cent of the latter. Viosterol in oil contains activated ergosterol in corn oil. This is rich in vitamin D, contains no vitamin A. Viosterol in halibut liver oil is halibut oil to which viosterol is added. It contains vitamins A and D. Halibut liver oil is the plain oil without added vitamin D. It is rich in A, weak in D. Other fish oils are added to halibut liver oil to increase vitamin D potency. Standardized cod-liver oil has no additions. "Cod-liver oil with viosterol" has added, irradiated ergosterol in corn oil.

Melitose. (Food Concentrates, Inc., Pier 3, New York City.) No. 1: ripe banana (dry). No. 2: ripe banana and dextrose malt extract. No. 3: milk sugar and ripe banana.

Mellin's Food. Wheat flour, wheat bran, malted barley, potassium bicarbonate.

Meringue. Egg, lemon, sugar.

Mince Meat. Formerly, a mixture of finely minced meat, suet, apples, raisins and other dried fruits, citron, molasses, sugar, spices and brandy or cider. Today the brandy and usually the meat and suet are omitted.

Mock Turtle. Diced veal with various vegetables, herbs, spices and lemon juice.

Moore's Food. Wheat, malt.

Muffets. Whole wheat.

Mulligatawny. Originally an East Indian soup whose name signifies "pepper water." Usually contains curry powder, meats, vegetables, mango, cocoanut, rice, cayenne pepper, etc.

Mull-Soy. (The Mueller Laboratories, 2935 Frederick Avenue, Baltimore, Maryland.) This is a vegetable milk substitute in liquid form containing soy bean, soy bean oil, dextrose, sucrose, minerals, corn oil and vitamin concentrates A and D (fish liver oil).

Mustard. Ground mustard or mustard flour, salt, vinegar.

National Biscuit Company Products. The following National Biscuit Company Products contain no milk or butter.

Crown Pilot	Famous Ginger Wafers	<i>Cereals</i>
Dandy Oysters	Ginger Snaps	Shredded Wheat
N.B.C. Sodas	Graham Crackers	Wheatsworth Whole
Oysterettes	Gentry Jumbles	Wheat
Premium Flake	Graham Wafers	Triscuit
Saltines	Jonnie	Triscuit Wafers
Saratoga Flakes	Kettle Cookies	
Uneeda Biscuit	Lemon Snaps	
Sky Flake Wafers	Mary Ann	
Ritz	Pantry Cookies	
N.B.C. Trentons	Toasted Dainties	
Pretzelettes	Zu-Zu Ginger Snaps	
Pretzenos	Wheatsworth Whole Wheat Grahams	
Cart-wheels	Fig Bar	
Chocolate Snaps		

Nestlé's Food. Malted whole wheat, malt, dry milk, wheat flour, cod liver oil.

New Pettijohn's. Whole wheat.

Nichol's Snow White S. Corn.

Noodles. Wheat and egg. Plain noodles as well as "egg noodles" may contain egg.

Nutro. Cereal and peanut flour.

Oat Bread. Oatmeal, wheat flour, potato, yeast, salt.

Oleomargarine. Usually contains cottonseed, peanut, or soya oil. It may contain some milk.

Olive Oil. Many brands of so-called olive oil are not pure olive oil but have added cottonseed oil, corn oil, etc. The Pompeian Olive Oil Company, Baltimore, states that "virgin pure Pompeian Olive Oil" is the first cold pressing of properly matured olives under controlled pressure.

Pabulum. Wheat meal, oatmeal, corn meal, yeast, beef bone, iron, salt, alfalfa.

Pâté de Foie Gras. Goose liver, truffles, spices. It may also contain pork, usually does.

Pepper Pot. Originally of the West Indies, this is a popular dish in various sections of the United States. Philadelphia pepper pot has as its base stewed tripe and small dumplings with pepper. Vegetables, especially okra, fish, etc., may be added.

Peter Pan Bread. White flour, sweetened condensed milk, lard, salt, malt extract, yeast, water.

Pillsbury's Vitas. Wheat.

Post Toasties. Hulled white corn grits, salt, sugar.

Post's Bran. Bran flakes and other parts of wheat flour—malt, syrup, salt.

Post's 40% Bran Flakes. Wheat bran, wheat, malt syrup, salt.

Postum. Wheat bran, wheat, molasses.

Postum Cereal. Whole wheat, bran, cane sugar, molasses.

Potato Chips. Fried in cottonseed oil.

Pumpnickel. Rye graham flour (20 per cent), bleached clear flour (80 per cent).

Malt (1/10 per cent), salt (1 per cent), caramel coloring (like molasses or chicory).

Purina Health Pancake Flour. Whole wheat, corn, phosphate of soda.

Quaker Crackels. Corn, wheat, oats.

Quaker Farina. Wheat.

Ralston Products. Ry-Krisp, see below. Ralston Wheat Cereal contains wheat, iron and calcium salts. Ralston Corn Flakes contain corn, salt, sugar and barley malt. Ralston Wheat Oats contains oats and wheat. Ralston Checker Rolled Oats contains oats. Baby Ralston contains wheat endosperm and wheat embryo with added iron and calcium.

Rice Biscuits. (Battle Creek Food Company.) Yeast extract, salt, sugar, rice.

Rice Bread. Wheat, rice, potato.

Rice Flakes. (Battle Creek Food Company.) Yeast extract, salt, sugar, rice.

Roman Meal. Ground flaxseed.

Root Beer. A fermented infusion of root bark and herbs containing essential oils such as sarsaparilla, birch, spruce, wild cherry, spikenard, wintergreen, anise, cassia, cloves, lemon, coumarin, vanilla, ginger, with sugar and yeast added.

Rum. Distilled from cane sugar products.

Rye Bread (Horlamus). See Horlamus.

Ry-Krisp. (Ralston Purina Company, St. Louis.) This contains whole rye, water and salt, no wheat, egg or milk.

Safe-Mix. (American Dietetics Co., Yonkers.) Contains soy and potato flours.

Salad Oil. Cottonseed oil.

Salmagundi. Chopped meat, fish, anchovies, onions, pickles, vinegar, pepper and other variable articles.

Salami. Pork, beef, grape juice, garlic, spices.

Sarsaparilla. Caramel, cologne spirits, oils of anise, orange, sassafras, wintergreen, powdered pumice stone, sugar, and water.

Sausages. Chopped meat, usually beef or pork, cured, spiced and stuffed in beef, sheep or hog casings. Saltpeter is added to retain the red color. There is great variation in method of preparation. Ingredients listed above vary, and can be counted upon to apply only for the high class products. Sausages often contain potato flour, rice and bread as binders.

Savita. (The Battle Creek Food Company.) Brewer's yeast, hops, parsley, leek, celery, onion, carrots, salt. This makes a nutritious bouillon.

Savoy and Moore's Food. Wheat flour and malt.

Schwarzbrot. Coarse X rye flour.

Scrapple. Pork, corn meal or buckwheat seasoned with spices and herbs.

Similac. (M. & R. Dietetic Laboratories, Columbus, Ohio.) Cow's milk, cod liver oil, cocoanut oil, olive oil, lactose.

Soy Condensed Milk. (The Battle Creek Food Company.) Soy bean, lactose, salt.

Soy Acidophilus Milk. (The Battle Creek Food Company.) Soy bean, lactose, salt.

Spaghetti. Wheat and milk.

Spices. The commoner spices have already been described. They may come from almost any portion of the plant. Ginger is a root stock; cinnamon an inner bark; cloves are flower buds; nutmeg a seed; black pepper the entire fruit; sage and thyme are leaves and upper parts of the plant. Ward lists the principal spices as follows:

Allspice	Cinnamon	Horseradish	Pepper (black)
Anise	Cloves	Mace	Pepper (red-green)
Bay leaves	Coriander	Marjoram	Saffron
Capers	Cumin	Mint	Sage
Caraway	Curcuma	Mustard	Savory
Cardamom	Dill	Nutmeg	Tarragon
Cayenne pepper	Fennel	Paprika	Thyme
Celery seed	Ginger	Parsley	Turmeric

Steinhardt's Infortina. Diastased cereals, dried milk, lactose, cane sugar.

Stokely's Strained Baby Cereal. Contains cereal grain, milk, soy bean, flour, salt and yeast. These are also constituents of Macy's Strained Cereal.

Tamale. Cornmeal, rice, pumpkin flour or rarely some other cereal; meat of any kind; chilis, garlic.

Tartar Sauce. Mayonnaise, capers, olives, cucumber, pickles.

Tortilla. Corn.

Tripe. The fatty inner lining of the stomach. Tripe is usually obtained from beef, although veal, sheep and hog tripe are used at times.

Tuna Fish. Packed in cottonseed oil.

Uncle Jerry's New England Corn and Rice Pancake Flour. Corn, wheat, potatoes, rice, salt and leavening.

Uncle Jerry's New England Self-Raising Buckwheat Flour. Buckwheat, wheat, corn, seasoning, leavening.

U. S. Health Food. Ground flaxseed.

Vienna Sausage. Pork, beef, spices stuffed in sheep or hog casings.

Vinegar. This very dilute acetic acid is formed in the acid conversion of alcohol. In the United States the term vinegar is usually applied to apple or cider vinegar. Other available vinegars are wine or grape vinegar; malt or beer vinegar also known as British

vinegar; sugar vinegar made from sugar or molasses; glucose vinegar from corn syrup; and "spirit" or white vinegar made from dilute alcohol. This last, white vinegar, pure dilute acetic acid, is available for those allergic to apple. The patient may make up his own from 28 per cent acetic acid (3 teaspoonfuls of 28 per cent acetic acid to the glass of water).

Wheat Substitute Flour. Horlamus Rye Bread, see Horlamus. C-D Special Flours (Chicago Dietetic Supply House, 1750 West Van Buren Street, Chicago) lists pure barley flour, corn flour, lima bean flour, oat flour, potato flour, rice flour, rye flour, soy bean flour, tapioca flour. C-D Soy Bean Wafers contain soy beans, cottonseed oil, salt and baking powder. C-D Soy Flakes contain soy bean and salt. C-D Barley Cookies contain barley flour, cottonseed oil, sugar, salt, baking powder, soda and vanilla. C-D Barley Wafers contain barley flour, cottonseed oil, salt, baking powder and soda. The Battle Creek Food Company prepares a pure soy bean flour, as does also Mead Johnson & Company. Safe-Mix contains soy and potato flours. See Safe-Mix. For other sources see Substitute Foods List.

White Bread. Bleached patent flour, sugar (2 per cent), salt (1 per cent), yeast ($\frac{1}{2}$ per cent), malt ($\frac{1}{10}$ per cent), eggs, vegetable oil, butter.

Whiskey. Distilled from malt, corn, rye and other cereals.

White Sauce. Butter, flour, milk, seasoning.

Whole Bran Shreds. Wheat bran, malt syrup, salt.

Whole Wheat Bread. Bleached patent flour (80 per cent), whole wheat flour (20 per cent), salt (1 per cent), eggs, sugar, caramel coloring.

Wines. Fermentation of fruit juices, usually grapes.

Worcestershire Sauce. There are a number of sauces of the Worcestershire type which vary in composition. A typical formula includes soy, vinegar, lime juice, onions, tamarinds, garlic, fish such as anchovies, or pickled herring, red chili and spices.

Notes on Special Recipes for Patients Allergic to Wheat, Egg or Milk

General instructions concerning wheat-substitute breads. In general, any recipe containing wheat flour may be used by substituting, for 1 cup of wheat flour:

1 cup of corn flour, rye flour, or rye meal.

A short cup of corn meal or rice flour.

$\frac{1}{2}$ cup of potato flour or cornstarch.

$\frac{3}{4}$ cup of buckwheat or soy bean flour.

$1\frac{1}{2}$ cups barley flour or ground rolled oats.

Combinations of substitutes produce better results than a single substitute. All substitutes require longer and slower baking than wheat-flour products, especially when making loaf bread. Coarse meals and flour require more leavening material. With these, $2\frac{1}{2}$ teaspoonfuls of baking powder should be used per cup of flour instead of the customary 1 teaspoonful per cup of wheat flour.

Starchy water such as potato or rice water makes a more moist loaf. Milk changes the flavor of the loaf, makes it richer in food value, and produces a more tender crumb and crust. Usually 1 cup of liquid is allowed for each loaf of bread, the size of a pan loaf. If the dough rises too long it will sour. Muffins are best made in small tins so that they will be rather crusty.

Rye meal is preferable to rye flour, since its taste is not as strong. In making muffins it may be substituted measure for measure for wheat flour, provided twice as much egg is used as is called for in the wheat recipe. Corn flour is preferable to corn starch and, as a thickening for sauces, may be used in the same proportion as wheat flour.

Notes on egg-free recipes.—One should be careful to avoid using baking powder containing egg. Royal, Calumet, and K. C. Baking Powders are egg-free. In using a standard recipe in which eggs are to be omitted, the prescribed amount of baking powder is added, plus 1 teaspoonful for each omitted egg.

Special recipes.—Many dietitians and patients have become interested in the preparation of wheat-, egg- and/or milk-substitute recipes. The patient who must avoid any or all of these should have no difficulty in finding adequate substitute breads. Pamphlets containing recipes may be obtained from the Bureau of Home Economics of the United States Department of Agriculture; the American Dietetic Association, 185 North Wabash Avenue, Chicago; The Ralston Purina Company, St. Louis; Mead Johnson Company, Evansville, Indiana; and the Chicago Dietetic Supply House, 1750 West Van Buren Street, Chicago. The following recipes should fulfill all needs. Boldface letters in parentheses following the headings indicate the foods (wheat, egg or milk), which are not included in the recipes.

GENERAL RECIPES*

The following wheat substitute recipes contributed by the writer's patients have been found satisfactory.

Rice Waffles (W)

2 cups rice flour
4 tablespoons melted butter
2 cups sweet milk
 $\frac{1}{2}$ teaspoon salt
4 heaping teaspoons baking powder
2 eggs separated
Fold in stiff whites last

This will serve four persons.

Rice Muffins (W)

1 cup rice flour
4 eggs beaten very light
1 pint sweet milk
5 teaspoons melted butter
3 heaping teaspoons baking powder added last

Bake in a quick oven
This will make 10 muffins.

Oatmeal Cakes (W-M)

1 egg
 $\frac{1}{2}$ cup sugar
 $\frac{3}{4}$ tablespoon melted butter
1 cup rolled oats
 $\frac{1}{2}$ teaspoon salt
 $\frac{1}{4}$ teaspoon vanilla

Beat egg until light. Add sugar. Stir in remaining ingredients. Drop by teaspoon on a thoroughly greased pan. Spread into shape with a case knife dipped in cold water. Bake in a moderate oven.

Rye Flour Raised Biscuits (W.E.M.)

1 potato, mashed
1 yeast cake
3 tablespoons sugar
1 teaspoon lard
3 level tablespoons salt
 $2\frac{1}{2}$ lbs. rye flour

Make sponge of potato, yeast, and sugar. Let rise one half hour. Add lard, salt, flour. Knead five minutes and let rise six hours. Put in pans, let rise again and bake forty minutes in moderate oven.

Rye Bread (W.E.M.)

Sponge

9 ounces water
9 ounces rye flour
 $\frac{1}{2}$ ounce compressed yeast

Dough

9 ounces water
25 ounces rye flour
 $\frac{1}{2}$ ounce salt

Mix sponge and let stand until it breaks (approximately $2\frac{1}{2}$ hours). Mix well and as soon as dough is light (which will require approximately 30 min.) make into loaves and place in greased pans. While rising moisten dough with a little water or milk to prevent crusting. (This should take about 40 min.) Bake 1 hour in a moderate oven.

Rye Muffins (W)

1 egg
2 cups milk
1 teaspoon salt
 $1\frac{1}{2}$ teaspoons baking powder
1 tablespoon butter
2 cups rye flour
Mix as ordinary muffins.

Rice Muffins (W)

2 eggs
2 cups milk
1 teaspoon salt
2 teaspoons butter (heaping)
2 teaspoons baking powder
3 cups rice flour
Mix as ordinary muffins.

The most satisfactory muffins are prepared with a mixture of rice and rye flours, since the rice flour is rather too dry and the rye too moist.

Gold Cake (Potato Flour) (W)

$\frac{1}{2}$ cup butter
1 cup sugar
Yolks of 6 eggs
1 teaspoon vanilla
 $\frac{1}{2}$ cup sweet milk
 $\frac{1}{2}$ teaspoon soda
1 teaspoon cream of tartar
 $1\frac{1}{2}$ cups potato flour

Beat butter and sugar to a cream, add beaten yolks, dissolve soda in milk and add. Stir in flavoring. Add flour sifted with cream of tartar. Bake in moderate oven.

*From Vaughan, Warren T.: Allergy and Applied Immunology, The C. V. Mosby St. Louis, 1934.

Sponge Cake (Potato Flour) (W-M)

4 eggs
1 cup sugar
 $\frac{1}{2}$ cup potato flour
1 teaspoon baking powder
1 teaspoon vanilla or lemon flavoring.

Beat whites and yolks separately, then mix, add sugar and flour, baking powder and vanilla. Beat thoroughly. Bake in a moderate oven.

Oatmeal Cookies (W-M)

2 cups brown sugar
 $\frac{1}{4}$ teaspoon salt
 $1\frac{3}{4}$ cups rolled oats
1 teaspoon baking powder
2 eggs
Butter size of egg

Cream butter and sugar, oatmeal, and baking powder. Mix well. Drop in small portions from spoon into large baking pan. Bake in moderate oven until brown. Do not put close together.

Potato and Rye Muffins (W)

2 eggs, well beaten
 $\frac{1}{4}$ cup potato flour
1 heaping teaspoon baking powder
 $\frac{3}{4}$ cup milk
1 cup rye flour
2 tablespoons butter
Cook in muffin tins

Rye Cakes (W-E)

2 cups rye flour
 $1\frac{1}{2}$ cups coconut, shredded
1 cup milk
 $1\frac{1}{2}$ cups sugar
2 tablespoons cocoa
1 teaspoon vanilla
Bake in cookie tins.

Rye Loaf Bread (W-E)

4 cups rye flour
 $\frac{3}{4}$ cup of rice flour
 $\frac{3}{4}$ cup any other substitute flour
1 cup riced potatoes, solidly packed
1 cake yeast (1 ounce)
1 teaspoon sugar
1 tablespoon salt
1 pint lukewarm sweet milk
1 teaspoon caraway seed may be added.

Pour milk in mixing bowl, add the sugar and yeast dissolved in $\frac{1}{4}$ cup of the lukewarm milk. Stir in the rest of the ingredients and knead until smooth and elastic. Let rise in a warm place and until double its bulk. Toss on board, form into loaves, place in pans and let rise again until double its bulk. Bake in a rather hot oven 1 hour or longer until well done. Brush top with water.

Buckwheat Bread (W-E)

A very passable raised bread may be prepared with pure buckwheat flour, using water or, preferably, milk. Baking soda or yeast may be used. The loaf is a bit heavy, and is best sliced thin and warmed, to be served as a "Toast Melba."

2 cups buckwheat flour
2 tablespoons sugar
 $2\frac{1}{2}$ teaspoons baking powder (Royal or K.C.)
Pinch of salt, to taste
1 teaspoon melted butter
 $1\frac{1}{2}$ cups water or milk

Potato Flour Muffins (W-M)

Separate the whites from the yolks of 4 eggs and beat the whites until they are very stiff and dry. Add a pinch of salt and 1 tablespoonful of sugar to the yolks, which have been beaten, and fold this mixture into the whites. Sift $\frac{1}{2}$ cupful of white-potato flour and 1 teaspoonful of baking powder together and fold into the egg mixture. Finally add 2 teaspoonfuls of ice water, turn into ungreased muffin pans and bake in a moderate oven—350° F. for fifteen or twenty minutes.

HOME ECONOMIC RECIPES*

Group A. Containing no wheat, milk, or eggs

Rye and Rice Flour Muffins (W-M-E)

$1\frac{1}{2}$ cups rye flour
 $\frac{1}{2}$ cup rice flour
2 teaspoons baking powder
 $\frac{1}{2}$ teaspoon salt

2 tablespoons sugar
 $1\frac{1}{2}$ cups water
2 tablespoons melted fat

Sift the dry ingredients together. Add the water and the melted fat. Mix thoroughly and bake in small sized greased muffin tins in a moderate oven (375° F.) for 25 minutes.

*Prepared by The Bureau of Home Economics, United States Department of Agriculture, Washington, D. C. Form 597.

Corn Meal, Rye, and Rice Flour Muffins (W-M-E)

1 cup corn meal	$\frac{1}{2}$ teaspoon salt
$\frac{1}{2}$ cup rye flour	2 tablespoons sugar
$\frac{1}{2}$ cup rice flour	1 cup water
6 teaspoons baking powder	2 tablespoons melted fat

Sift the dry ingredients together. Add the water and the melted fat. Beat thoroughly and bake in small greased muffin tins in a moderate oven (375° F.) for 20 to 30 minutes. This mixture may also be baked in small loaf pans in a moderate oven for 30 minutes.

Rice Flour and Corn Meal Muffins (W-M-E)

1 $\frac{1}{3}$ cups rice flour	$\frac{1}{4}$ cup sugar
$\frac{2}{3}$ cup corn meal	1 cup water
4 teaspoons baking powder	$\frac{1}{4}$ cup melted fat
$\frac{1}{2}$ teaspoon salt	

Sift the dry ingredients together. Add the water and the melted fat and beat for about 3 minutes. Bake in small greased muffin tins in a moderate oven (375° F.) for 20 to 30 minutes.

Steamed Brown Bread (W-M-E)

1 cup rye flour	1 cup quick oatmeal
1 cup corn meal	$\frac{3}{4}$ cup molasses
$\frac{1}{4}$ teaspoon soda	1 cup water
1 teaspoon salt	

Sift the rye flour, corn meal, soda and salt together. Add the oatmeal and mix thoroughly. Add the molasses and water, stir until well mixed. Fill greased molds not more than two-thirds full and steam 3 $\frac{1}{2}$ hours. The covers should be greased before being placed on the molds.

These quantities of ingredients make three ten-ounce can loaves.

Rye and Rice Flour Bread (W-M-E)

3 tablespoons sugar	$\frac{2}{3}$ cup warm water
$\frac{3}{4}$ teaspoon salt	1 cup rice flour
2 cakes compressed yeast	1 cup rye flour
3 tablespoons fat	

Mix the sugar, salt, yeast, and fat with the warm water. Add the sifted flour and stir until a dough is formed. Knead thoroughly, grease the dough, cover, and let rise in a warm place (80° F.) until double in bulk. Knead again and mold into loaves, grease the dough, cover, and let rise again. Bake in a moderately hot oven (400° F.) for 5 minutes then lower to 350° F. for 40 minutes.

Rye Flour and Corn Meal Bread (W-M-E)

1 cup corn meal	$\frac{1}{2}$ cup corn sirup
2 teaspoons salt	1 cake yeast softened in
1 pint boiling water	1 tablespoon warm water
3 cups rye flour	

Cook the corn meal and salt in the pint of boiling water for 15 minutes. Cool and add the rye flour, sirup, and softened yeast. Mix thoroughly and let rise in a warm place (80° F.). Mold and place in pans to rise again. Bake in a moderate oven (375° F.) for 40 minutes. This bread is best served hot, although it makes very good toast when cold.

These quantities of ingredients make two loaves.

Rye Bread (W-M-E)

Sponge	Dough
1 $\frac{1}{4}$ cups warm water	2 teaspoons salt
2 $\frac{1}{2}$ cups sifted rye flour	2 cups warm water
1 cake yeast	6 $\frac{1}{2}$ cups sifted rye flour

Mix the sponge and let stand in a warm place (80° F.) until it breaks (approximately 2 $\frac{1}{2}$ hours). For the dough, dissolve the salt in the 2 cups of water and add alternately with

the flour to the sponge. Mix well and let rise in a warm place (80° F.) until the dough is light (about 30 minutes). Make into loaves and place in greased pans. Moisten the dough with a little water to prevent the formation of a crust and let rise for about an hour. Bake in a moderate oven (375° F.) for 1 hour.

These quantities of ingredients make 3 pounds of bread.

Pineapple Upside Down Cake (W-M-E)

$\frac{2}{3}$ cup sugar	4 teaspoons baking powder
$\frac{1}{3}$ cup fat	1 cup water
1 cup rye flour	2 tablespoons fat
1 cup rice flour	2 tablespoons brown sugar
$\frac{1}{2}$ teaspoon salt	6 slices pineapple

Cream the sugar and $\frac{1}{3}$ cup of the fat and add the sifted dry ingredients and water alternately. Melt the 2 tablespoons fat and 2 tablespoons brown sugar in a baking or frying pan. Place 6 slices of pineapple on this mixture and pour over it the cake batter. Bake in a moderate oven (375° F.) for 45 minutes. This cake is best when served hot.

Spice Cake (W-M-E)

1 cup brown sugar	1 teaspoon nutmeg
$1\frac{1}{4}$ cups water	1 teaspoon cinnamon
1 cup seedless raisins	1 cup fine corn meal
2 ounces citron, cut fine	1 cup rye flour
$\frac{1}{3}$ cup fat	4 teaspoons baking powder
$\frac{1}{2}$ teaspoon salt	

Boil the sugar, water, fruit, fat, and salt together in a saucepan for 3 minutes. When cool add the spices, baking powder, and flour which have been sifted together. Mix thoroughly and bake in a greased loaf-pan in a moderate oven (375° F.) for about 45 minutes.

Rice Flour Cookies (W-M-E)

1 cup sugar	$\frac{1}{2}$ teaspoon salt
$\frac{1}{2}$ cup fat	1 lemon rind, grated
$2\frac{1}{2}$ cups rice flour	2 tablespoons lemon juice
4 teaspoons baking powder	$\frac{3}{4}$ cup water

Creám the sugar and fat and mix with the sifted dry ingredients and the lemon rind. Add the lemon juice and water to make a firm dough. Drop by spoonfuls onto a greased baking sheet and pat into shape. Sprinkle with sugar and bake in a moderate oven (385° F.) for about 7 minutes.

Group B. Containing no wheat or eggs.

Include Group A. Also the following

Rye Flour and Soy Bean Flour Biscuits (W-E)

2 cups rye flour	6 teaspoons baking powder
1 cup soybean flour	1 teaspoon salt
4 tablespoons fat	$1\frac{1}{4}$ cups milk

Sift the dry ingredients together, cut in the fat with a biscuit cutter. Add the milk slowly and when a soft dough is formed, place on bread board floured with rye flour, press into a sheet about $\frac{1}{2}$ inch thick, cut into small rounds, place on a biscuit pan and bake for 12 minutes in a very hot oven (450° F.).

To make drop biscuits add $\frac{1}{2}$ cup milk to recipe and drop the mixture by teaspoonfuls on a greased pan and bake in a very hot oven (450° F.) for 12 minutes.

Rice flour may be substituted for rye flour in the above recipe.

Rye and Rice Flour Crisp (W-E)

2 cups rye flour	1 teaspoon soda
1 cup rice flour	$1\frac{1}{2}$ cups sour milk
$1\frac{1}{2}$ teaspoons salt	

Sift the dry ingredients together. Add the milk, mix well and place the dough on a well floured board, roll very thin and cut into strips 3 inches by $1\frac{1}{2}$ inches. Bake in a moderately hot oven (385° F.) for about 18 minutes.

These quantities of ingredients make 75 crisps.

Rice Flour Gingerbread (W-E)

2 cups rice flour	$\frac{3}{4}$ cup quick oatmeal
1 teaspoon soda	1 cup molasses
1 tablespoon ginger	1 cup sour milk or buttermilk
$\frac{1}{2}$ teaspoon salt	$\frac{3}{8}$ cup fat, melted

Sift the flour, soda, ginger and salt together. Add the oatmeal and mix thoroughly. Add the molasses, milk, and the melted fat. Beat thoroughly. Pour into a greased cake pan and bake in a moderate oven. (350° F.) for 30 minutes.

Group C. Containing no wheat or milk.

Include Group A.

Include Groups B and D, replacing the sweet milk with water.

Potato Starch Sponge Cake (W-M)

4 eggs	$\frac{3}{4}$ cup sugar
1 tablespoon lemon juice	$\frac{1}{2}$ cup potato starch
	$\frac{1}{4}$ teaspoon salt

Beat the yolks of the eggs until they are light and creamy. Add the lemon juice and sugar. Beat well. Sift the starch and salt together and fold into the mixture. Then fold in the stiffly beaten whites, pour into an ungreased cake pan and bake in a very moderate oven (325° F.) for 45 minutes. Remove from the oven, turn the pan upside down on a rack, and let the cake drop out itself.

Jelly Roll.—Pour the batter into a long cake pan and bake for 20 minutes. Remove from pan, cover with tart jelly and roll at once.

Rice Flour Pudding (W-M)

2 eggs	$\frac{1}{4}$ teaspoon salt
$\frac{3}{4}$ cup sugar	$\frac{1}{2}$ teaspoon cinnamon
3 tablespoons rice flour	1 cup chopped figs
1 teaspoon baking powder	1 cup chopped nuts

Beat the eggs until light and creamy. Add the sugar gradually, beating constantly. Add the sifted dry ingredients, then the chopped nuts and figs, beat thoroughly. Pour into a medium sized greased cake pan and bake in a slow oven (300° F.) for 40 minutes. This pudding may be served with ice cream or with any sauce.

Rice Flour Fig Bars (W-M)

1 cup figs	1 tablespoon melted fat
1 cup nuts	1 tablespoon lemon juice
1 cup powdered sugar	$\frac{1}{4}$ cup chopped figs
2 eggs	$\frac{1}{2}$ teaspoon salt

Chop the figs and nuts together. Add the sugar and beaten eggs, mix well. Add the fat, lemon juice and flour sifted with the salt. Beat well. Spread the mixture $\frac{1}{4}$ inch deep in a greased shallow cake pan. Bake in a moderate oven (325° F.) for about 40 minutes. Cut into strips and if desired roll in powdered sugar.

These quantities of ingredients make 20 bars.

Group D. Containing no wheat.

Include Groups A, B, and C.

Rice Flour Waffles (W)

1 $\frac{3}{4}$ cups rice flour	1 $\frac{1}{2}$ cups milk
3 teaspoons baking powder	2 eggs
1 teaspoon salt	3 tablespoons melted fat

Sift the dry ingredients together, add the milk and beaten egg yolks, then the melted fat. Fold in the stiffly beaten whites of the eggs and cook the waffles in a hot waffle iron. These quantities of ingredients make 6 waffles.

Buckwheat flour may be substituted for rice flour.

Griddle Cakes.—The above proportions may be used for griddle cakes, with the exception of buckwheat flour in which case add $\frac{1}{2}$ cup milk.

Rice Flour and Potato Starch Waffles (W)

$\frac{3}{4}$ cup rice flour	$1\frac{1}{4}$ cups milk
1 cup potato starch	2 eggs
3 teaspoons baking powder	3 tablespoons melted fat
1 teaspoon salt	

Proceed as for rice flour waffles.

Griddle Cakes.—The same proportions may be used for griddle cakes.

Rice Flour and Potato Starch Muffins (W)

1 cup rice flour	1 egg
$\frac{3}{4}$ cup potato starch	1 cup milk
1 teaspoon salt	3 tablespoons melted fat
3 teaspoons baking powder	

Sift the dry ingredients together. Beat the egg slightly, add the milk. Stir gently into the dry ingredients. Add the melted fat and bake in medium sized muffin tins in a moderate oven (400° F.) for 30 minutes.

These quantities of ingredients make 12 muffins.

One-fourth cup of soy bean flour may be substituted for the potato starch.

Corn Meal and Potato Starch Muffins (W)

$\frac{2}{3}$ cup corn meal (white)	$\frac{1}{2}$ teaspoon sugar
$\frac{1}{3}$ cup potato starch	1 egg
2 teaspoons baking powder	$\frac{1}{2}$ cup water or milk
$\frac{1}{2}$ teaspoon salt	1 teaspoon melted fat

Proceed as for rice flour and potato starch muffins.

Date Pudding (W)

$\frac{1}{2}$ cup fat	4 teaspoons baking powder
1 cup sugar	$\frac{1}{4}$ teaspoon salt
2 eggs	$\frac{1}{4}$ teaspoon nutmeg
1 cup milk	1 cup chopped dates
$1\frac{1}{4}$ cups rice flour	6 whole pitted dates
$\frac{3}{4}$ cup soybean flour	

Cream the fat. Add the sugar and the well beaten eggs. Add alternately the milk and the sifted dry ingredients. Stir in the dates. Arrange the 6 dates in a design on the bottom of a well greased mold and pour in the batter very carefully so as not to move the dates. Cover and steam $2\frac{1}{2}$ hours. Serve hot with lemon or hard sauce.

The same proportions may be used for a date loaf cake. Pour the batter into a greased loaf pan. Bake in a moderate oven (350° F.) for about 50 minutes.

Fig pudding may be made by substituting figs for the dates.

CORN RECIPES***Corn Meal Mush With Cheese (W-M)**

For this dish yellow corn meal is generally used, and the cheese may be added just before the mush is taken from the fire. For a mush made with 1 cup of yellow corn meal the usual allowance is one half cup, or 2 ounces, of grated cheese. There is, however, no limit to the quantity of cheese which can be added, and the addition of the cheese tends to make not only a more highly nitrogenous and nourishing dish but also one which can be eaten without the addition of butter or cream. Like the ordinary corn meal mush, it is often fried either in deep fat, after having been egged and crumbed, or in a small amount of fat, or baked.

Crackling Bread (W-E-M)

For each cup of corn meal allow three fourths teaspoon salt and half a cup of cracklings, the crisp brown particles that are left after lard is rendered. If the cracklings contain a great deal of fat, place them while warm in a piece of cheesecloth and squeeze out part of the fat. Pour boiling water over the meal till it is of such consistency that it can be mashed with the hand. Add the cracklings, shape into cakes, and bake.

*Follows Bulletin No. 1236 United States Department of Agriculture.

Crisp Corn Meal Cake (W-E)

3 cups milk	1½ cups corn meal
1 teaspoon salt	

Mix the ingredients and spread on shallow buttered pans to a depth of about one-fourth of an inch. Bake in a moderate oven until crisp.

This will serve 6 persons.

Sour-Milk Corn Bread (W)

2 cups corn meal	1½ teaspoons salt
2 cups sour milk	2 eggs
2 tablespoons butter	1 teaspoon soda
2 tablespoons sugar, white or brown	1 tablespoon cold water

There are two ways of mixing this bread, and also those in the four following recipes, all of which include milk and eggs. By the first method the meal, milk, salt, butter, and sugar are cooked in a double boiler for about 10 minutes. When the mixture is cool the eggs, well beaten, are added, and the soda, dissolved in the water. By the other method all the dry ingredients, including the soda, are mixed together, and then the sour milk and eggs well beaten and the butter are added. If the second method is followed the cold water is not needed. The bread should be baked in a shallow iron or granite pan for about 30 minutes.

Since the bread made by the first method is of much better texture, that method is to be preferred except in cases where there is not time for the necessary heating and cooling of the meal.

Buttermilk may be substituted for the sour milk, in which case the butter should be increased slightly; or sour cream may be used and the butter omitted.

This serves 6 persons.

Spider Corn Bread (W)

1½ cups corn meal	3 teaspoons baking powder
2 cups sour milk and	1 teaspoon salt
1 teaspoon soda;	2 eggs
or	2 tablespoons butter
1½ cups sweet milk and	

Mix as in the preceding recipe save that the fat should be used to grease an iron spider. Heat the spider, pour in the batter, and bake on the middle shelf of a hot oven.

Southern Corn Muffins (W)

These are made like the spider corn bread in the preceding recipe save that 2 cups of corn meal are used and the dough placed in hot, greased iron muffin pans and baked about 20 minutes in a fairly hot oven.

Spoon Corn Bread (W)

2 cups water	1 tablespoon butter
1 cup milk	1 teaspoon salt
1 cup white corn meal	2 eggs

Mix as directed for sour-milk corn bread (see above). Add the eggs well beaten and the other ingredients. Beat thoroughly and bake in a well-greased pan for 25 minutes in a hot oven. Serve from the same dish with a spoon.

This serves 6 persons.

Corn Meal Puffs, Griddlecakes, and Waffles

The peculiar granular consistency of corn meal, which is a disadvantage under some circumstances, is an advantage in making such dishes as griddlecakes and waffles, for it renders them very tender.

Corn Meal Puffs (W)

1 pint milk	½ teaspoon salt
½ cup corn meal	4 eggs
4 tablespoons sugar	(Grated nutmeg (if desired))

Cook the milk and meal together 15 minutes with the salt and sugar. When cool, add the eggs well beaten. Bake in cups. Serve with stewed fruit or jam. This serves 6 persons.

Corn Meal Fritters (W)

By increasing the corn meal in the preceding recipe to one-half cup, the batter is made stiff enough to be dropped into hot fat and fried. This serves 6 persons.

Corn Meal and Meat Dishes

A number of dishes are made of meat or fish in which corn meal mush is used, or which resemble mush in some particulars. Recipes for such dishes follow:

Corn Meal Mush With Pork (W-E-M)

1 pound lean pork, part meat and part bone	1 teaspoon salt
1 cup corn meal	$\frac{1}{2}$ teaspoon powdered sage
	Water

Cook the pork in water until the meat can be removed easily from the bone. Remove the meat, cool the broth, and remove the fat. Reduce the broth to about a quart, or add water enough to bring it up to this amount, and cook the corn meal in it. Add the meat finely chopped and the seasonings. Pack in granite bread tins. Cut into slices and fry. Beef may be used in the same way. This serves 6 persons.

Roast Pork With Batter Pudding (W)

A dish corresponding to the Yorkshire pudding which is frequently served with roast beef can be made out of corn meal to serve with roast pork.

$\frac{1}{4}$ cup corn meal	$\frac{1}{2}$ teaspoon salt
1 cup milk	2 eggs

Place the milk, corn meal, and salt in the top of a double boiler and cook about 10 minutes, or until the meal has expanded to form a mixture. After the mixture has cooled, add the eggs, well beaten. Grease gem tins thoroughly, allowing to each about 1 teaspoon of fat from the roast pork. Bake in a moderate oven, basting occasionally with the drippings of the pork.

This serves 4 persons.

Corn Meal Fish Balls (W)

2 cups cold white corn meal mush	1 egg
1 cup shredded codfish	1 tablespoon butter

Pick over the codfish and soak it to remove salt, if necessary. Combine the ingredients and drop by spoonfuls into hot fat. Drain on porous paper. These codfish balls compare very favorably in taste with those made with potato and are prepared more easily and quickly. The mush must be as dry as possible.

This makes 12 fish balls.

Indian Pudding (W-E)

5 cups milk	1 teaspoon salt
$\frac{1}{3}$ cup corn meal	1 teaspoon ginger
$\frac{1}{2}$ cup molasses	

Cook milk and meal in a double boiler 20 minutes; add molasses, salt, and ginger; pour into buttered pudding dish and bake 2 hours in slow oven; serve with cream.

This serves 8 persons.

Corn Meal and Fig Pudding (W)

1 cup corn meal	1 cup finely chopped figs
1 cup molasses	2 eggs
6 cups milk (or 4 cups of milk and 2 cups of cream)	1 teaspoon salt

Cook the corn meal with 4 cups of milk, add the molasses, figs, and salt. When the mixture is cool, add the eggs, well beaten. Pour into a buttered pudding dish and bake in a moderate oven for 3 hours or more. When partly cooked add the remainder of the milk or the cream without stirring the pudding.

This serves 8 or 10 persons.

Corn Meal and Apple Pudding (W)

For the figs in the preceding recipe substitute a pint of finely sliced or chopped sweet apples.

This serves 8 or 10 persons.

Hominy Turnover (W)

1 pint cooked coarse hominy	2 well-beaten eggs
1 cup milk	1 tablespoon fat
1 teaspoon salt	

Mix all together. Turn into a frying pan in which the fat has been melted. Stir until hot throughout. Let it cook until golden brown on the bottom, then fold like an omelet and serve on a hot platter. This is suitable for the main dish at supper or luncheon.

Hominy and Bean Cakes (W-E)

1 cup boiled coarse hominy	$\frac{1}{2}$ cup milk
1 cup cooked red kidney beans	1 tablespoon fat
$\frac{1}{2}$ teaspoon cayenne pepper	1 teaspoon salt
$\frac{1}{2}$ tablespoon cornstarch	

Make a white sauce from the last five ingredients by melting the fat, blending it with the cornstarch, salt and pepper, adding the milk, and cooking until thickened. Grind the hominy and beans through a food chopper, mix with the white sauce, form into cakes, and brown in a little fat. Such cakes may take the place of meat occasionally.

Boiled Hominy Grits (W-E-M)

1 cup hominy grits	2 teaspoons salt
5 cups water	

Add the grits slowly to the salted boiling water. Boil 10 minutes over fire, then place in the fireless cooker and allow to remain overnight, or cook for 2 hours in a double boiler.

The grits may be poured while warm into a dish or molds, cooled, and served with fruit or preserves for a simple dessert, or they may be cooked in deep pans, sliced, and fried.

Hominy Muffins (W)

1 cup cold boiled hominy grits	2 teaspoons baking powder
1 cup sweet milk	$\frac{1}{2}$ teaspoon salt
1 egg	1 tablespoon melted fat
$1\frac{1}{4}$ cups corn flour	

Beat the milk and egg into the hominy grits, add the melted fat and dry ingredients. Mix well and bake in well-greased muffin pans for 30 minutes.

This makes 12 muffins.

Corn Meal and Hominy Bread (W)

1 cup corn meal	1 tablespoon melted fat
1 cup boiled hominy grits	1 teaspoon baking powder
1 cup milk	$\frac{1}{2}$ teaspoon salt
1 egg	

Beat the milk and egg into the hominy grits, add the melted fat and dry ingredients, and mix well.

This batter may be baked in a greased pan and served with a spoon from the dish in which it is baked as a spoon bread, or it may be cooked on a griddle and served as griddle cakes.

Hominy Date Pudding (W-E)

1 cup hominy grits	$\frac{1}{2}$ cup sugar
5 cups milk (skim or whole)	1 cup chopped seeded dates
1 teaspoon salt	1 teaspoon vanilla

Add the salt and hominy grits to the milk and cook in a double boiler one hour. Add sweetening, dates, and vanilla, and mix well. Partially cool before serving.

Fruit Scallop (W-E)

$1\frac{1}{2}$ cups cooked hominy grits	1 tablespoon sugar
1 cup stewed apricots	$\frac{1}{2}$ tablespoon butter
$\frac{1}{2}$ cup apricot juice	

In a greased baking dish place first a layer of the hominy grits which have been mixed with the fruit juice, then a layer of the fruit. Repeat until dish is nearly full. Dot over with the butter and sprinkle with 1 tablespoon of sugar mixed with cinnamon. Bake until brown. Serve hot or cold with sauce or top milk.

Peaches, pears, and other fruits may be used instead of apricots.

Chocolate Pop Corn (W-E-M)

2 cups white sugar
 $\frac{1}{2}$ cup corn syrup

2 ounces chocolate
 1 cup water

Put these ingredients into a kettle and cook them until the syrup hardens when put in cold water. Pour over 4 quarts of crisp, freshly popped corn and stir well to insure the uniform coating of the kernels.

Sugared Pop Corn (W-E-M)

Make a syrup by boiling together 2 cups of granulated sugar and 1 cup of water. Boil until the syrup strings from the spoon or hardens when dropped into cold water. Pour over 6 quarts of freshly popped corn and stir well.

Pop-Corn Balls (W-E)

1 pint syrup
 1 pint sugar

2 tablespoons butter
 1 teaspoon vinegar

Cook till the syrup hardens when dropped into cold water. Remove to back of stove and add one-half teaspoonful of soda dissolved in a tablespoonful of hot water and then pour the hot syrup over 4 quarts of freshly popped corn, stirring till each kernel is well coated, when the mixture can be molded into balls or into any desired form.

Maple syrup makes light-colored balls, while darker ones are made with New Orleans molasses.

Corn Chowder (W-E)

1 cup fresh corn
 $1\frac{1}{2}$ inch cube salt pork, diced
 1 onion, sliced
 1 quart potatoes, sliced

1 cup milk or cream
 Salt and pepper
 8 crackers

Fry the salt pork, add the onion, and cook until the onion is tender. Boil the potatoes 5 minutes in 1 quart of boiling water, add the fat, and cook until the potatoes are soft. Add the corn and milk and bring to the scalding point. Add the butter and seasoning. Pour over the crackers and serve hot.

DISHES CONTAINING RICE*

Many find ordinary polished rice as usually served very unpalatable. It has little taste and is rather too pasty for many. Brown rice and especially Indian rice or wild rice are on the contrary quite tasty and distinctly more nutritious.

Boiled Rice (W-E-M)

1 cup rice
 2 quarts boiling water

2 teaspoons salt

Look the rice over, remove any foreign materials, wash in hot water, and drain. Add the rice gradually to the rapidly boiling salted water. Then reduce the heat so that the rice boils gently, and cook with the pan uncovered until the grains are tender and have no hard center when pressed between the thumb and finger. (Rapid boiling breaks the kernels and cooking at a temperature below boiling allows them to absorb so much water that they become sticky.) Drain at once in a colander or sieve and pour hot water through the rice to remove loose starch and separate the grains. Cover with a cloth and set over hot water on the back of the stove, or place in a warm oven for a short time. The kernels will continue to swell. One cup of uncooked rice yields about $3\frac{1}{2}$ cups of boiled rice. To reheat rice for serving, steam it in a colander or sieve over boiling water just long enough to heat it through.

Cook brown rice in this same way, except that after boiling gently for about 30 minutes, cover, and simmer until it is cooked through and the water is absorbed. Brown rice does not become sticky.

If a softer, moister cooked rice is desired, as for croquettes, patties, or rice ring, cook it in a double boiler, fireless cooker, or waterless cooker. Use about 2 cups of water to 1 of rice, and when the rice is tender drain it but do not rinse with hot water.

Minerals in the water in some sections of the country cause boiled rice to have a grayish or greenish cast. A pinch of cream of tartar in the cooking water prevents this discoloration.

To cook wild rice, cover with cold water, add salt, and boil for 20 to 25 minutes. Drain, remove cover, and let the rice steam dry on the back of the stove.

*Leaflet No. 112 United States Department of Agriculture.

Rice in Soup

Rice is much used in making soups. It is added to white or brown stock, vegetable soup, chicken soup, and others. The proportion generally used is one-half cup of cooked rice or 3 tablespoons of uncooked rice to each quart of soup. Wash uncooked rice well, add to the soup, and simmer one-half hour in a covered pan. Rice cooked in the soup has a more savory flavor, although it makes the soup slightly cloudy.

Rice Patties and Rice Ring

Boil rice until it is very soft; drain, but do not rinse.

For rice patties, press the hot cooked rice into a layer about an inch thick in a shallow pan. Cut out rounds with a biscuit cutter, place in a buttered pan, drop a bit of butter on the top of each pattie, and brown in a hot oven (about 400° F.), or under a broiling flame. One cup of uncooked rice makes 12 patties.

For rice ring, pack the hot cooked rice into a ring mold which has been rinsed in cold water, and place in a moderate oven for about 5 minutes. To serve, loosen around the edges, turn a large round hot platter or plate over the mold, and invert quickly. Or hot rice may be arranged in a ring on a platter with a tablespoon and broad knife, but the outline is not so regular as when the ring mold is used.

Especially delicious to serve with rice patties or rice ring is creamed chicken; or creamed dried beef or other meat, fish, oysters, eggs, or mushrooms; or mixed vegetables in a sauce flavored with cheese, curry, or some other savory seasoning. A ring mold of creamy rice makes an attractive dessert when the center is filled with fruit topped with whipped cream.

Rice Croquettes (W)

$\frac{3}{4}$ cup uncooked rice	1 tablespoon lemon juice
2 tablespoons minced parsley	1 teaspoon salt
4 tablespoons butter	White or cayenne pepper
1 egg, beaten	Egg and crumbs
Few drops onion juice	Fat for deep frying

Cook the rice as boiled rice, drain but do not rinse, and cool. Or use 2 cups of left-over boiled rice. Cook the parsley in the butter, and add to the rice. Then add the egg and seasonings, mix well, and mold into croquettes. Roll in beaten egg, and then in fine bread crumbs. Heat the fat in a deep kettle to 350° F., or until a cube of bread browns in 40 seconds. Place 2 or 3 croquettes at a time in a frying basket and lower slowly into the hot fat for about 2 minutes, or until they are a golden brown. Remove and drain on absorbent paper. Serve while hot with cold meats or creamed dishes, or with jelly or preserves.

Rice Baked With Tomatoes and Cheese (W-E)

1 cup uncooked rice	$\frac{1}{2}$ cup chopped pimientos
2 cups canned or fresh sliced tomatoes	Salt and pepper
$\frac{3}{4}$ cup grated cheese	

Boil the rice until tender and drain. Combine with the remaining ingredients, and bake in a greased baking dish for 30 minutes in a moderate oven (350° to 370° F.). Serve hot.

Rice Pilau (W-E-M)

$\frac{1}{4}$ cup finely diced salt pork	$\frac{1}{2}$ cup chopped celery
$\frac{3}{4}$ cup uncooked rice	4 tablespoons minced parsley
$\frac{1}{2}$ cup chopped onion	Salt, pepper, and paprika
3 cups hot water	

Fry the salt pork until slightly browned. Add the rice, which has been washed and drained, and the onion, and stir until the rice is a golden brown. Then gradually add the hot water, cover, and cook until the rice is becoming tender. Then add the remaining ingredients; place in a greased baking dish and bake for 30 minutes in a moderate oven (350° to 370° F.). Serve hot from the baking dish.

Curried Rice (W-E-M)

1 cup uncooked rice	3 cups boiling water or meat stock
2 tablespoons fat	1 to 2 tablespoons curry powder
1 tablespoon chopped onion	2 teaspoons salt

Wash the rice and drain. Heat the fat in a frying pan, add the rice and onion, and stir until the rice is golden brown. Add the boiling water or meat stock and seasonings. Cover and cook slowly for about 30 minutes until the rice is tender.

Rice Stuffing for Meats or Fowl (W-E-M)

2 cups boiled rice	4 tablespoons butter or other fat
2 tablespoons chopped onion	$\frac{1}{2}$ teaspoon savory seasoning
1 tablespoon chopped parsley	Salt and pepper to taste
1 cup chopped celery and leaves	

Cook the onion, parsley, and celery in the fat for a few minutes. Add the rice and seasonings, and stir until well mixed and hot, and use as the stuffing in chicken, duck, or other fowl, or in boned cuts of meat. Any kind of rice, white, brown, or wild rice, may be used in stuffing.

Creamy Rice (W-E)

Rice cooked in milk or in a mixture of half milk and half water is creamy and has a pleasing, delicate flavor and higher food value than when cooked in water alone. Creamy rice is good as a breakfast cereal or as a dessert with sugar, flavorings, spices, fruits, or chopped nuts. If cooked until the kernels are very soft and the liquid is absorbed, creamy rice is especially attractive molded, chilled, and served with fresh or preserved fruits.

For cooking in a double boiler, use 4 to 5 times the volume of liquid to rice. Season to taste with 1 to $1\frac{1}{2}$ teaspoons salt to each cup of uncooked rice. For cooking over direct heat use 5 to 6 times the volume of liquid to rice. Boil gently and stir occasionally to prevent sticking.

Baked Creamy Rice Pudding (W-E)

3 tablespoons uncooked rice	$\frac{1}{2}$ teaspoon nutmeg or cinnamon
1 quart milk	$\frac{1}{2}$ teaspoon salt
$\frac{1}{3}$ cup sugar	$\frac{1}{2}$ cup raisins, if desired

Wash the rice, and stir into the remaining ingredients. Pour into a baking dish, and bake for from $2\frac{1}{2}$ to 3 hours in a slow oven (250° to 300° F.). Stir 3 or 4 times during the first hour. The creaminess and delicious flavor of this pudding are due to the long slow cooking.

Rice and Pineapple Cream (W-E)

$\frac{1}{3}$ cup uncooked rice	$\frac{1}{3}$ cup sugar
$\frac{1}{2}$ cup water	1 cup whipped cream
2 cups milk	1 cup canned shredded pineapple
$\frac{3}{4}$ teaspoon salt	

Wash the rice, and soak it half an hour in the water and milk. Add the salt and bring to boiling over direct heat. Then cook in a double boiler for 40 minutes, or until the rice is soft and the mixture is thick. Stir in the sugar, and heat for a few minutes longer. Remove from the heat and cool. Fold in the pineapple and whipped cream and chill before serving; or if preferred, pour the mixture into a mold which has been rinsed in cold water, and then chill. Other fruits drained from their juices may be used if desired, and one-half cup of shredded coconut is a good addition.

SOYA BEAN PREPARATIONS***Soya Bread (Makes 1 Loaf) (W-M)**

1 cup white refined soya flour	$\frac{2}{3}$ cup water
$\frac{1}{2}$ teaspoon salt	4 egg whites
2 teaspoons baking powder	4 egg yolks
1 tablespoon lard or butter	

Combine the flour, salt, baking powder, lard, water and egg yolks. Fold into this the stiffly beaten egg whites. Pour into greased loaf tin and bake slowly 30 to 40 minutes.

Soya Pancakes (W-M)

5 tablespoons white refined soya flour	1 egg yolk
$\frac{1}{2}$ teaspoon salt	1 egg white, beaten stiff
$\frac{1}{2}$ grain saccharine	Sufficient water to moisten

Mix flour, salt, and saccharine. Add the egg yolk and sufficient water to moisten. Into this fold the stiffly beaten egg white. Fry on hot griddle with oil or fat.

*Prepared by Mead Johnson & Company, Evansville, Indiana, from whom white refined soya flour may be obtained.

Corn Meal—Soya—Mashed Potato Muffin (W)

$\frac{1}{2}$ cup corn meal	1 teaspoon salt
$\frac{1}{2}$ cup white refined soya flour	$2\frac{1}{2}$ tablespoons shortening
$\frac{1}{2}$ cup milk	1 cup mashed potatoes
$\frac{1}{2}$ teaspoons baking powder	1 egg
$1\frac{1}{2}$ tablespoons syrup	

Add shortening, syrup, milk and beaten egg to mashed potatoes. Sift all dry ingredients together and add to the other mixture. Divide evenly into twelve greased muffin tins. Baking time: 30 minutes. Oven temperature: 375° F.

Corn Flour—Soya Muffins (W)

$\frac{3}{4}$ cup corn flour	1 teaspoon salt
2 tablespoons white refined soya flour	$1\frac{1}{2}$ tablespoons melted shortening
$\frac{1}{2}$ cup buttermilk	$\frac{1}{4}$ teaspoon soda
$2\frac{1}{2}$ teaspoons baking powder	1 egg

Beat egg. Add buttermilk, shortening, and salt. Sift dry ingredients and add to liquid, mixing all ingredients together well. Pour batter into six greased muffin tins and bake 25 minutes in oven at 375° F.

Rolled Oats—Soya Muffins (W)

$\frac{7}{8}$ cup rice flour	$\frac{3}{4}$ teaspoon salt
$\frac{1}{4}$ cup white refined soya flour	1 tablespoon oil
$1\frac{2}{3}$ cup milk	1 egg
5 teaspoons baking powder	2 cups rolled oats
1 tablespoon syrup	

Heat milk to scalding point and pour over rolled oats. Let stand one-half hour. Add well beaten egg, syrup, and oil. Then add the dry materials which have been sifted together. Beat hard. Turn into well oiled muffin pans and bake in moderate oven for 30 minutes. Baking time: 30 minutes. Oven temperature: 375° F.

General appearance is rough, with dark crust. This is a moist, heavy or rather filling muffin.

Rice Soya Muffins (W)

1 cup rice flour	1 teaspoon salt
$\frac{1}{4}$ cup white refined soya flour	3 tablespoons melted butter
1 cup milk	1 egg
3 teaspoons baking powder	

Sift all dry materials. Beat egg. Add milk and melted shortening. Add dry ingredients to liquid and stir just enough to combine ingredients. Divide evenly into eight well-greased muffin tins and bake about 30 minutes in oven, 400° F.

Corn Flour—Soya Muffins (W)

1 cup corn flour	1 teaspoon salt
$\frac{1}{4}$ cup white refined soya flour	3 tablespoons melted shortening
1 cup milk	1 egg
3 teaspoons baking powder	

Sift all dry ingredients together. Beat egg until light. Add milk and melted shortening and add to dry ingredients. Mix only enough to mix thoroughly. Pour into greased muffin tins and bake. Makes eight muffins. Baking time: 20 minutes. Oven temperature: 400° F.

100% Soya Muffins (W)

$\frac{3}{4}$ cup white refined soya flour	4 egg whites (beaten stiff)
$\frac{1}{2}$ teaspoon salt	2 tablespoons milk powder—skimmed
1 teaspoon baking powder	$\frac{3}{4}$ cup water
4 egg yolks (beaten)	

Blend and sift the flour, salt, and baking powder together. Beat the egg yolks. Mix all the water into the blended ingredients until smooth. It will make a thick paste. Add the beaten egg yolks to this and mix well. Fold the stiffly beaten egg whites into the above mixture. Do not mix—fold until smooth. Bake in muffin tins or rings at about 400° to 425° F. The above will make about twelve small muffins.

Soya Oatmeal Cookies (W)

$\frac{3}{4}$ cup rice flour	$\frac{1}{2}$ teaspoon salt
1 cup rolled oats	$\frac{1}{2}$ cup shortening
6 tablespoons white refined soya flour	1 egg
4 tablespoons milk	$\frac{1}{2}$ teaspoon cinnamon
$\frac{1}{2}$ teaspoon soda	$\frac{1}{2}$ teaspoon nutmeg
$\frac{1}{2}$ teaspoon baking powder	1 teaspoon vanilla
1 cup brown sugar	

Cream sugar and shortening until light and fluffy. Add rolled oats. Add alternately the dry ingredients (which have been sifted together) and the milk. Add the well beaten egg last. Drop, about two inches apart, a teaspoon of the batter on a well greased baking sheet and bake 20 minutes at 375° F. One-half ($\frac{1}{2}$) cup each of pecans, dates, and coconut may be added if you care for them.

100% Soya Cookies (W)

$\frac{3}{4}$ cup white refined soya flour	4 tablespoons butter or shortening
$\frac{1}{2}$ teaspoon salt	3 eggs (well beaten)
$\frac{1}{2}$ teaspoon baking powder	$\frac{1}{2}$ cup water or milk

Blend and sift the flour, salt, and baking powder together. Beat the eggs until light and add milk. Cream the butter or shortening into the flour as for pie crust. Then add the well beaten eggs and make a dough. Turn out on floured board and roll to one-eighth inch thickness. Cut with cookie cutter and put on a greased pan. Baking temperature: About 400° F.

Potato Starch—Soya Sponge Cake (W-M)

$\frac{1}{2}$ cup potato starch flour	$\frac{1}{2}$ teaspoon salt
2 tablespoons white refined soya flour	1 tablespoon lemon juice
$\frac{1}{4}$ cup sugar	4 eggs

Beat egg yolks until thick and lemon colored. Add lemon juice, salt and sugar and beat again. Sift potato flour, soya flour and baking powder together. Stir into egg and sugar mixture. Beat egg whites until stiff and fold into the batter. Pour into ungreased loaf cake tin and bake thirty minutes at 375° F. May be baked in sheet cake and spread with tart jelly and rolled, making a delicious jelly roll. If baked in loaf pan, allow to cool in pan which has been inverted on cake rack. Cake will fall from pan of its own accord.

Rice Flour—Soya Butter Cake (W)

1 $\frac{1}{2}$ cups rice flour	$\frac{1}{2}$ teaspoon salt
2 tablespoons white refined soya flour	$\frac{1}{2}$ cup butter
$\frac{1}{2}$ cup milk	2 eggs
1 $\frac{1}{2}$ teaspoons baking powder	1 teaspoon vanilla
$\frac{1}{4}$ cup sugar	

Cream sugar and butter together. To this add beaten eggs. Sift dry ingredients together and add to creamed mixture alternately with milk. Add flavoring. Pour batter into greased cake pan, 8 x 8 x 2, and bake 30 minutes at 400° F. Allow to set in pan a few seconds when removed from oven before turning out on rack.

Soya Sponge Cake (W-M)

$\frac{3}{4}$ cup rice flour	6 eggs
2 tablespoons white refined soya flour	1 teaspoon cream of tartar
$\frac{1}{2}$ cup water	1 teaspoon lemon extract
1 cup sugar	$\frac{1}{2}$ teaspoon salt

Beat egg yolks until lemon colored. Add sugar, salt and water, and beat until creamy. Sift measure of flour. Sift into egg yolk and sugar mixture and mix thoroughly. Beat egg whites until foamy. Add cream of tartar and finish beating until stiff. Add well beaten egg whites and extract to batter and mix thoroughly. Pour into ungreased pan and bake 30 minutes at 400° F. After removing from oven, invert pan until cake is cool, at which time carefully remove from pan.

PART VII

POLLENS AND POLLINOSIS, AND OTHER INHALANT ALLERGY

Latet anguis in herba

—MORELL MACKENZIE

CHAPTER XL

POLLEN DEVELOPMENT

Historical. Nine hundred years before Christ, the ancient Assyrians recognized a difference between specimens of date palms which might be termed sexual. They had discovered that to assure date production the female tree must be fertilized by dusting it with the branches of the male tree. Herodotus described this practice upon his return from his travels in the East in the fifth century B.C. Pliny, the Roman who styled himself not as a naturalist but as a "compiler of anecdotes," of whose wide interest in natural history we have seen evidence in the discussion of foods, stated that all trees and even herbs have two sexes. Actual investigation of the significance of these deductions was not initiated until about A.D. 1700. Camerarius (1694) stated his belief that the stamens are the male sexual organs. Kölreuter (1761) demonstrated insect transmission of pollen. Sprengel (1812) showed that crossed pollination rather than self-pollination is the rule. He proved the importance of insects as vectors, and distinguished between insect and wind pollination. He recognized that flowers whose pollen was *anemophilous* (wind loving) were less showy or attractive and contained no nectar to attract insects, as is present in *entomophilous* (insect loving) plants.

The word pollen is derived from the Latin and means *fine flour*. Its existence was recognized long before its significance or function was appreciated.

Anatomy of flowers. Pollen granules are formed in the anthers, the male sexual organs, of plants. They correspond to the sperm cells of animals. Their function is to fertilize the ovum, in the seed. This is essential to reproduction.

The different pollen granules vary considerably in size, shape, and general conformation.

The poet, Goethe, was one of the first to recognize that a flower consists of a group of specialized and highly differentiated leaves arranged in four series. The firm greenish leaves covering the bud and found at the base of the flower are called "sepals" and are grouped in a circle to form the calyx. The calyx exists to give protection and support to the flower.

The next inner group of differentiated leaves is the corolla (meaning small crown) made up of the petals of the flower. Sometimes, as in the primrose, this circle is of but a single layer; sometimes, as in the cultivated rose, it has several layers. These brightly colored petals attract insects. The honey and the nectar

are found at their bases. The poinsettia flower illustrates the evolution of petal from leaf. In this plant the red petals are identical in size and shape with the green leaves farther down on the stem.

On pulling back the petals of most flowers, such as the buttercup, for example, one will see a circle of threadlike structures standing erect, with nodular tips, surrounding a larger central organ with a clustered head. The former represent the third series of modified leaves and are the stamens, carrying on their tips the anthers in which the pollen granules are formed. The central structure, the fourth of the modified leaf system, is the pistil with its terminal carpel which contains the ovaries of the flower.



Fig. 94.—Sagittal section of a tulip, showing component parts. From left to right: the petal, which is a modified leaf; stamen, which is divided into filament (lower half) and anther (upper half), where pollen is produced; and pistil. There are three stamens in the figure. In the pistil, the fluted top is the stigma, the shaft is the style, at the base of which is the ovary. The nectary, source of nectar, is at the base, in the angle between stamens and pistil.

In such a flower as the buttercup there should be no difficulty in the migration of the pollen granules for the short distance from anther to carpel. But Nature has ordered that plants which fertilize themselves, often do not flourish. Many plants are self sterile. Even though they have stamens and pistils, they do not fertilize themselves. Darwin realized the importance of cross-pollination when he showed that continued self-fertilization produced an inferior fruit while cross-fertilization improved its quality. As a consequence, many plants are so

arranged that the pollen grains will not fertilize their own ovaries. This is established in a variety of ways. Sometimes the pollen grains mature at different times from the structures of the carpel so that the grains do not find lodgment on the stigma but must be carried to other similar plants which have matured somewhat earlier. Sometimes the male and female reproductive structures are found on different parts of the plant and not in the same flower, as in the buttercup, and sometimes they are entirely separated, being found on different plants.

So, as a rule, even when the male and female elements are present in the one flower, facilities must be at hand for fertilization from one flower to another. This can be accomplished through the intermediary of insects or by the wind. As I have said, the brightly flowering plants usually have heavy sticky pollen and depend upon the insects for its transport. So important is the bee in cross-fertilization that cherry growers sometimes lease apiaries which they move into their orchards at the beginning of the blooming period, and apple orchardists contract with beekeepers to furnish bees when the trees are in bloom.

Bees are interested in gathering pollen almost to the same extent as nectar. They use it as a food and store it in large quantities in the open cells of the brood combs. It is the source of protein food for the larvae of the growing bees. This may explain some of the cases of allergy from the eating of honey. While the severe illness of certain persons resulting from the sting of a bee might possibly be due to pollen introduced with the sting, there is evidence that one may be specifically allergic to the bee protein itself and this appears to be the more logical explanation.

Where wind pollination occurs, it is obvious that tremendous amounts of pollen must be produced in order that a very minute fraction will reach its destination on the pistils of the female flower. Those who have walked through the fields during the pollinating season or even the more urban individual whose only contact on foot with the country is the golf course will realize the tremendous amount of pollen produced. If the early morning golfer, whose ball has carried him into the rough, strikes some of the larger grasses, such as the plantain or timothy, he will dislodge a veritable cloud of pollen which will float away on the breeze. One who has walked through a field of grass or weeds at the right time (usually early on a dry sunny morning) will find his trousers legs quite covered with a yellowish coating of pollen dust.

Even the trees shed tremendous amounts. A tree in the process of pollination when shaken may emit clouds of dust almost as thick as the smoke from a fire. On account of this, in certain sections, the paper mulberry is called "the smoking mulberry."

One should not confuse the pollen with the seed. The pinhead-sized seed of the dandelion attached by a rather long stalk to its white cottony parachute which carries it on the wind is not the pollen. Pollination occurred long before the dandelion went to seed and is the yellow material which as a child you rubbed onto your chin. "Rub a dandelion on your chin and if your chin becomes yellow you like butter, otherwise you don't." As a matter of fact, your gastronomic proclivities play no part. The dandelion did or did not happen to be pollinating when it was rubbed against the chin.

Some pollens have wings, stationary wings like those on an air glider which carry them many, many miles; but these are microscopic and are not to be confused with the winged seeds of trees, such as the maple, ash, or linden.

Small as it is, the pollen grain is not a single cell but usually contains from two to four cells and is both vitalistically and chemically a most complex substance. It is a spore, and capable of continuing to live as such for a remarkably long period and under adverse circumstances. It contains the elements of life and when joined with the reproductive cell of the ovum will reproduce in all of its entirety the plant from which it came. Chemically, it contains many substances, chief among which are proteins, cellulose, glucosides, starches, sugars, and enzymes or ferments. Pollen grains from different plants vary enough so that in a very general way the plants they came from can be identified by examination of the pollen under the microscope. Thus, the grass pollens as a class are smooth-walled, spherical or somewhat pear-shaped, often somewhat irregular in shape due to indentations on the surface. They remind one somewhat of a round clay ball into which a child had pressed his fingers at various places. The indentations are sometimes fairly round and sometimes long enough to be described as infoldings. The fresh grass pollen is often smooth and spherical without the indentations or infoldings, which presumably make their appearance in the course of drying. While the grass pollens have smooth surfaces, the pollens of the *Ambrosiaceae*, which include the ragweeds, false ragweed, marsh elder, sunflower, aster, daisy, and goldenrod, present rough or spiny surfaces reminding one of a cocklebur with very short spines. The chenopods, such as lamb's-quarters and thistle, and the amaranths produce pollen which is spherical with small round indentations giving somewhat the appearance of a dimpled golf ball. Tree pollens vary quite definitely among themselves and are in most instances different enough to be fairly closely identified.

The Wodehouse Worlds. Under the microscope, pollen grains are often remarkably beautiful and of startlingly intricate architectural detail. This is especially so with many of the entomophilous pollens. The anemophilous are usually simpler of design. One is inclined to wonder at the significance of these intricate patterns. Wodehouse has contributed an adequate and most interesting explanation.

He divides the world of living substances into three general groups. The first is *the world of gravity walkers*. On account of gravity, the larger the animal the more difficult is its locomotion. Its adjustment to the limitations imposed by gravity determine in a measure its form. An extremely large animal such as the whale would be so restricted by gravity that locomotion on land would be nearly impossible. It is therefore compelled to live in water which supports much of its bulk. At the other extreme Wodehouse places the mouse, about the smallest animal whose weight or gravity attraction enables it to maintain traction for its feet.

There is a natural tendency towards symmetry of design in all living things. Without gravity this symmetry would extend in all directions. But with man and animals and with trees and flowers the pull of gravity necessitates changes in form in this one direction, to counteract the force. Trees and flowers send their roots down and their stalks upward in conformity to the line of force. Since they are fixed objects the tendency toward symmetry persists in all other planes. But in man and animals another force, that of locomotion, further differentiates the being into front and rear. Evidence of the natural tendency toward symmetry therefore persists only laterally.

Wodehouse's next world, somewhat freed from gravitational activity, is *the world of easy flight*, the world of insects. Here, as in the world of gravity

walkers, gravity and movement impose the same type of bilateral symmetry. Insects are so small that they are relatively uninfluenced by gravitational effect and therefore cannot develop sufficient traction for walking. Their feet are therefore provided with suction discs or hooks. With these they may walk vertically up a wall or even upon the ceiling. Flight is the rule rather than the exception. Even so, there is some gravitational effect and insects must employ muscular effort to remain aloft. They do not float.

The third world described by Wodehouse, the world in which we find pollens and fungus spores, is termed *the world of floating and sticking things*. No wings are needed, because gravity is not sufficient to counteract the buoyant effect of air currents. In these objects we find no differentiation in form, in the direction of gravity, and no front or rear. Complete symmetry in all directions is the rule and is one of the directing forces controlling the development of the many beautiful patterns of the grain.

Anemophily and Entomophily.—Pollen grains vary in size from that of the pumpkin which has a diameter of about 200 microns to that of the forget-me-not (2.5 microns). It is almost entirely in the middle ranges, between 17 and 58 microns, that the floating or anemophilous pollens are found. Those larger than 58 are too heavy. They are influenced by gravity. Their problem is solved in that not being floaters they are stickers. They are entomophilous. So also are the very small pollens. Wodehouse suggests that this may be because, in view of their very small size, with consequent relatively tremendous surface area, the cohesive force makes discharge from the anthers difficult and interferes with separation of the grains from each other. This suggestion finds support in the mechanism of discharge of the paper mulberry. This is an extremely small pollen (13 microns) but is anemophilous. The flower contains a coil-spring-like mechanism which is released as the flower opens and forcibly ejects the pollen. This phenomenon may be seen with the unaided eye, as it occurs almost explosively, discharging such quantities of pollen as to give the appearance of a puff of smoke. Once having been discharged, these well-separated pollens become floaters.

There are smaller worlds. *The world of bacteria* comprises so much smaller organisms that morphologic differentiation is developed only to a limited degree. Still smaller is *the world of colloids* with objects so small as to be quite free from gravitational influence; objects which so far as can be determined are perfectly symmetrical spheres. The smaller the mass the larger becomes the relative surface area. The surface area of a thousand toy balloons each holding one cubic foot of air is enormous as compared with that of a single balloon containing one thousand cubic feet. With substances as small as colloids, the surface area is tremendous. As a consequence most of what is known of colloid chemistry deals with phenomena based upon the action of surface areas.

Anatomy of the pollen grain.—Returning to pollens, in the world of floating things, we are now in a position to understand how the tendency of nature to the production of perfect symmetry has wide freedom for action. How does this manifest itself and by what mechanism are so many different symmetrical patterns produced?

The pollen grain consists primarily of two portions, the intine, the living internal cellular structure, the active element in fertilization; and the exine or protective coating. The latter is chiefly responsible for the "sculpturing" or architectural appearance of the individual grain. At one or more locations

on the exine there are pores, the germinal pores through which the tube of protoplasm will eventually pass out to fertilize the ovum. These pores are found at the base of larger furrows or clefts, where the exine is very much thinned. The furrows serve a double function, that of forming a base for the germinal pore, and of providing for variation in the size of the grain. When the grain is moist, it is swollen, more nearly spherical, and the furrow is either shallow or nonexistent. When the grain is dry, as when caught on oil or glycerin or vaseline in routine pollen counting, the furrows appear as deep depressions. They provide flexibility in size and shape. It is this flexibility which causes the sometimes startling difference in appearance of the same pollen grains when observed in water and in oil. (Figs. 123 and 159.)

TABLE XXX. AVERAGE SIZE OF COMMON POLLEN GRANULES

(AFTER WODEHOUSE)

NAME	SIZE OF POLLEN	NAME	SIZE OF POLLEN
	IN MICRONS		IN MICRONS
Acacia	48—55	Maple	28—36
Alder	19—27	Marsh elder	18—20
Ash	20—25	Mesquite	22—32
Aspen	24—37	Mexican tea	23
Beech	40	Mountain cedar	18—22
Bermuda grass	34—36	Oak	25 × 31
Birch	20—40	Olive	22
Black walnut	31—34	Orach	20—27
Box elder	28—36	Orchard grass	28—36
Canary grass	40—46	Palmer's amaranth	23—25
Cattail	18—26	Paper mulberry	13
Chestnut	14 × 10	Pecan	44
Cocklebur	22—29	Pigweed	23—25
Common mugwort	18—28	Pine	45—65
Corn	90—100	Privet	28—30
Cottonwood	27	Red cedar	22—25
Curley dock	28—32	Redtop	25—31
Cypress	27—31	Russian thistle	28
Dandelion	24—27	Rye grass	62 × 40
Date palm	24 × 12	Sagebrush	25—28
Elm	23—38	Sheep sorrel	22—24
English plantain	25—40	Short ragweed	18—19
English walnut	42—48	Southern ragweed	20—21
False ragweed	18—23	Spiny amaranth	23—30
Fescue grass	31—37	Sweet gum	38
Giant ragweed	16—19	Sweet vernal grass	38—46
Goldenrod	17—26	Sycamore	14 × 18
Greesewood	24—30		to
Hazel	22—26		17 × 21
Hickory	40—52	Timothy	32—36
Hornbeam	25—41	Tumbleweed	24
Johnson grass	40—55	Velvet grass	28—34
June grass	28—32	Western ragweed	22—25
Kochia	29—34	Western water hemp	21—28
Lamb's-quarters	28	Wheat	48—57
Linden	28 × 36	White mulberry	17 × 21
Low spear grass	25—27	Willow	18

As the pollen grains develop in the anther, the nucleus of each mother cell divides into four. The four nuclei migrate to remote parts of the cell. Gradually the protoplasm constricts to separate them off into four pollen cells. They remain for a time in contact, as tetrads, held by small protoplasmic filaments. When these filaments finally break they determine the position of the germinal pore.

In some plants the tetrads remain attached (see photomicrograph of cattail pollen) but as a rule, they eventually separate. The exine is not formed by the protoplasm of the germ cell but is laid upon the surface by the surrounding tissues in the anther whose activity thus in great measure determines the sculpturing.

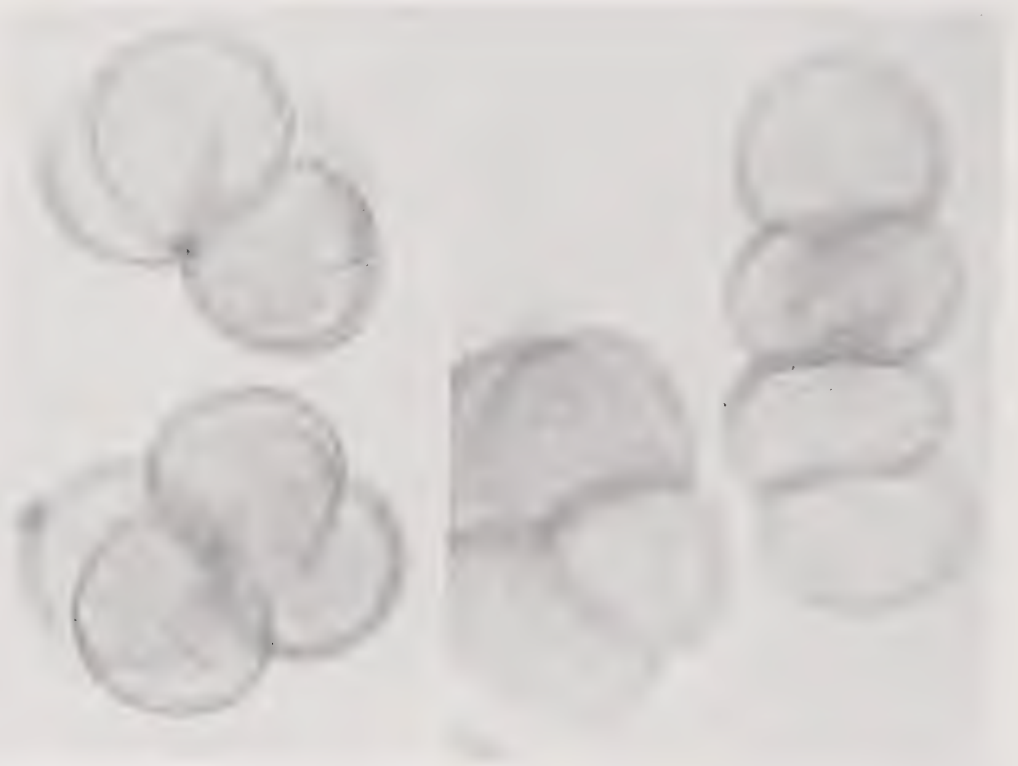


Fig. 95.—Tetrad formation. Examples of variations in the tetrad grouping as observed in cattail pollen

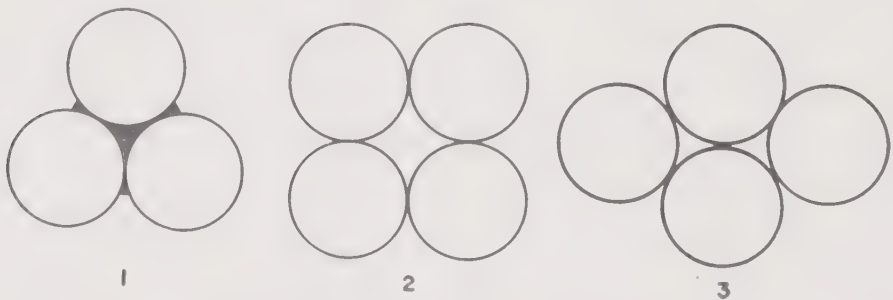


Fig. 96.—Tetrads. Possible basic combinations of four spheres in contact (tetrahedral, square, rhomboidal). In the first, each sphere is in contact with three others. Such pollen arrangement would account for three germinal pores. In the second, each is in contact with two while in the third, two are in contact with three, while the remainder are in contact with but two. In the last, half would have three germinal pores, half two. (After R. P. Woodhouse, "Pollen Grains," New York, 1935, McGraw-Hill Book Company.)

Pores and furrows. The number of germinal furrows and pores is determined chiefly by the arrangement of the primitive pollen grains in the tetrad. Fig. 96 indicates three possible arrangements. The tetrahedral is commonest. In it each cell is in contact with three others. Most pollens have three germinal furrows. In the rhomboidal arrangement two cells are in contact with three cells each, while the other two are only in contact with two each. Here one would anticipate that half the cells will have three sym-

metrically disposed furrows while the other half will have but two. Instead of two, four usually develop. With two the grain would be asymmetrical and the presence of two on one side appears to determine the evolution of two on the other side, not at points of original contact, whose purpose is the establishment of symmetry. So also in the square arrangement, although there should be two furrows there are more often four.

Wodehouse further shows how, depending upon the number and location of the primary germinal furrows, at points of contact in the developing pollen grains, all observed pollen configurations may result.

Beautiful sculpturing is seen only in entomophilous grains. This is due to deposition of exine upon the reproductive cells. Variations in configuration of anemophilous pollen are dependent chiefly upon the number and position of germinal pores and furrows. Some varieties have spiculated pollen, others indentations in the exine and still others such as the pine have special organs which will be discussed, but in none do we see the remarkable sculpturing that is observed in some of the insect-borne pollens.

Fertilization.—The pollen grain is always unicellular at first but the nucleus later divides. One nucleus controls the development of the pollen tube while the second is the generative nucleus. This latter divides again into two nuclei which pass out through the pollen tube as it develops, to reach the ovary. There, only one enters to fertilize the ovum.

When pollen is deposited on the stigma, at the tip of the pistil the base of which contains the ova, the protoplasmic germinal tube or pollen tube grows out through a germinal pore. It gradually elongates, making its way down the interior of the style in the pistil. It either passes along a naturally open canal, or in certain plants, works its way between cells in a mass of loose connective tissue, or, in still other types, directly penetrates the cells which it must pass through. The tube procures its nourishment from the surrounding structures of the pistil and reaches its destination in a surprisingly short time. Within twelve hours it may reach an ovum thirteen inches away. In most flowers no such great distance must be traversed.

The pollen tube is attracted toward the ovary by some chemotactic substance. An extract of a flower will *in vitro* attract the pollen tube from the same plant while the extract of a different species will repel it.

Longevity.—The life of the pollen grain is not long. Although date pollen has been said to be viable for fifteen years, most pollen under normal conditions is short lived. June grass pollen lives one day, English plantain eleven days and beech forty-one days.

CHAPTER XLII

POLLEN DISTRIBUTION

Anemophily and entomophily.—According to Wodehouse, primitive pollination was by the simple direct method of wind dispersal. This is true of primitive flowering plants such as the cycads, sago palms, the maidenhair tree, and the pines. It is an extravagant method, only one of many thousand grains ever reaching its destination. In contrast to the gymnosperm, the more highly developed angiosperm at some time in remote history undertook an experiment in insect pollination. Although it is probably fallacious to imply motivation in the evolution of plants, the story of the development of a pollination method can be easily followed by adopting the terminology of Wodehouse.*

“It is not exactly known how the angiosperms came to abandon wind pollination, but it was probably because insects at some very early period developed the habit of feeding on pollen. This, we may see going on today. For example, the corn plant, which is wind pollinated, is freely visited by bees which rob it of its pollen. The gymnosperm, like maidenhair tree and the pine, appear to have been able to fortify their pollens against this menace, possibly by producing unpalatable pollen or producing it so fast that they get it matured and shed before the insects can breed their numbers up sufficiently to devour it. This appears to be the primary reason why the majority of the anemophilous plants have only a brief flowering period. Other plants appear to have turned this adversity to their advantage; instead of combating the onslaught of insects, they encouraged their visits because the uneaten pollen which they accidentally carried from flower to flower proved to be quite as effective in achieving pollination as vast quantities discharged into the air. Through a long process of evolution, the plants appear to have developed a nectar to supply the insects, that they might spare their pollen, and by concealing the nectar in devious ways and placing the pollens at certain vantage points in the flowers, much pollen was saved at the cost of only a little nectar. But in order that this method may succeed it is necessary to have the right kinds of insects visit the flowers at the right times. It is obviously to secure this end that the elaborate and beautiful structures of flowers have been developed, always directed toward the most effective pollination with the minimum expenditure of pollen.”

However, in many instances this method failed because some insects, unable to secure the nectar normally, do so by biting a hole through the flower. They do not come in contact with the pollen. Also, the wrong kind of insect attempting to enter too small an orifice tends to split the flower open, and fails to establish crossed-fertilization.

As a consequence, some plants were highly successful in evolving a type of flower appropriate for insect fertilization while others were unsuccessful, finding it necessary to return to wind pollination. This latter group appears to include the grasses, the sedges and most, if not all, of the other angiosperms which are today wind pollinated.

Angiosperms and gymnosperms.—Thus we see that some angiosperms which represent the highest and most recent evolutionary members of plant life still distribute their pollen in the more elementary manner used by the gymnosperms. They have tried insect pollination but have been unable to adapt themselves to it and have reverted to the much more wasteful wind pollination. The angiosperm (*angion*, vessel—*sperma*, seed) is a plant whose seed is covered, the ovules being enclosed in an ovary and fertilized by way of the stigma and through the length of the pistil. The gymnosperm (*gymnos*, naked—*sperma*, seed) is a plant in which the ovules are not enclosed in an ovary. The pines belong in this latter group.

Angiosperms which have reverted to wind pollination probably once had color, perfume and nectar, those attributes which attract insects, but have

*Wodehouse, R. P.: Pollen Grains, McGraw-Hill Co., New York, 1935.

since lost them in great measure. Examples are the grasses and sedges whose vestigial flowers indicate that they are closely related to the lily family.

The poplars and willows, closely related, are interesting in this regard. The poplar appears to have reverted completely and is now solely wind pollinated. The willow still has perfume, nectar and more conspicuous flowers and is still pollinated by insects but also by the wind. The willow appears to be in a process of reversion, not yet completed.

Plants which have been forced to abandon insect pollination have been eminently successful in their return to wind pollination. This includes such as the ragweeds, the grasses, the sagebrushes, pigweed, lamb's-quarters and many of the forest trees.

Spendthrift pollination.—An idea of the tremendous wastefulness of wind pollination may be gained by the following observations which have been collected by Thommen from the literature and from his own experience. A single ragweed plant produced 8 billion pollen grains per square foot of field surface during the active stage of pollination. An average city lot of ragweed is capable of producing one hundred ounces of the pollen in a season. This would amount to about 60 pounds per acre. An area of 400 square feet of giant ragweed produced more than a pint of pollen in three days. According to Durham, at least a million tons of ragweed pollen are produced in the United States each season. This, piled together, would form a pyramid as high as a fifty-story office building, with its base over 1000 feet broad.

Distances to which pollen is carried.—Tree pollen has been found 34 miles from land, having been deposited on ships at this distance at the rate of 215 grains per square millimeter on the plate surface per day. Plates exposed in airplanes over Lake Michigan, thirty miles from shore, were found at times to contain almost as much pollen per cubic yard of air as at the same altitude over Chicago.

Pine pollen has been carried 400 miles, and pollen known to have come from Alaska has been deposited in Washington and Oregon.

Abbott Smith (1868) described a hay fever victim who on a boat far from land developed symptoms when the sails which had previously been furled were raised. He believed that pollen grains were liberated with the dust from the sails.

Erdtman, using special apparatus, has recovered pollen in the center of the Atlantic just above sea level. Studies of the dissemination of fungi also indicate the great distances to which particulate matter may be carried through the air. Stackman who first used the airplane for this purpose about fifteen years ago found barberry rust 16,000 feet in the air. He found that rust spores could be blown from northern Texas to Minnesota in 48 hours. Meier reported that fungi were collected in stratosphere flights 36,000 feet above the earth, remaining viable at minus 78° C. Colonel Lindbergh on his North Atlantic flight of 1933 found that air currents play a part in the distribution of pollen and spores between the northern lands. Meier observed over Central American waters (1935) that air at low levels (150 to 200 feet) might be almost sterile of spores due to rain washing, while at an altitude of 8,000 to 14,000 feet in the same vicinity fungi and bacteria were easily cultivated.*

Pollen clouds.—Grass pollen has been caught in airplanes as high as 17,000 feet. Not infrequently there is a higher concentration at an altitude of 4,000 to 6,000 feet than nearer the surface of the ground. These pollen

*Discussion of Committee on Aerobiology.

clouds result from air currents. Under appropriate conditions, we may have pollen showers from the pollen clouds as we do showers of water. In 1873 there was a shower of pollen in St. Louis, following which the ground appeared as though it had been sprinkled with sulphur. It was believed that this pine pollen had been brought 400 miles. Similar showers have been described in Switzerland and elsewhere in Europe.

Thommen suggests that the existence of pollen clouds may explain the increase in symptoms after sunset in spite of the fact that the ragweed plant sheds its pollen in the early hours of the morning. After sunset the air currents descend, carrying pollen with them. A similar phenomenon would explain the increase in symptoms at storm periods and during the prevalence of cold winds.

Pollen conservation, insect vectors.—This wasteful distribution of anemophilous pollen is to be contrasted with the mechanisms developed for the conservation of pollen from entomophilous plants. It has been known since the time of Aristotle that bees tend to visit but one kind of flower at a time, even though there are many varieties in a garden. A bee can carry almost one-third of its weight in pollen. In one study it was found that 28 of 32 bees carried a pure load of but one kind of pollen. The twenty-ninth had two varieties and the thirtieth had three. The pollen being sticky and adherent to insects' bodies, relatively small amounts need be available for fertilization. In contrast to the profusion described above, a dandelion generates less than 250,000 grains, a peony about 3,500,000 and an entire rhododendron plant about 73,000,000 in a season.

Potential importance of entomophilous plants.—Nevertheless these numbers are appreciable. Pollinosis due to entomophilous plants is infrequent as compared with that due to anemophilous. But the former does occur. The exposure must be much closer. Sunflowers growing in the back yard, rambler roses outside the window, cut flowers, roses, goldenrod and others inside the house, wisteria outside the window, all have been shown responsible for true hay fever. If one will test regularly for allergy to this type of plants one will be surprised how often positive reactions are observed. Some may be group reactions due to sensitization to a botanical family, but often careful discussion with the patient will demonstrate that these insect-pollinated plants actually cause symptoms. In a series of hay fever patients the writer found that for every 100 positive skin reactions to short ragweed, there were 32 to sunflower, 30 to goldenrod, 24 to daisy, 2 to dahlia, 22 to dandelion, 1 to apple and 18 to rose. Not all of these indicated actual sources of trouble, but questioning and observation indicated that several did.

In the writer's experience the situation is rather similar to that with occasional foods. The minor allergic is sensitized to foods with which he comes into occasional contact. The major allergic is sensitized to foods with which he comes into frequent or daily contact. In addition, the latter is sensitized to occasional foods and in the same degree as the former. Therefore, the major allergic should be tested not only with frequent offenders but also with the occasional offenders.

Similarly, with the pollens one should test not only with the commonly recognized allergenic anemophilous pollens, but also with the pollens of those entomophilous plants concerning which there is suspicion in the patient's history.

Meteorologic factors in pollen distribution and prevalence. The pollen distribution into the air in any one locality of any section of the country depends first upon the local flora. Ragweed pollen will not be in the air beyond

the limits of air transport in areas where ragweed is not growing. Topographic and other factors within the United States produce widely different types of vegetation in different sections.

Life zones.—The flora varies from subtropical to Hudsonian and even arctic-alpine in the high altitudes of the western mountain ranges. Some plants exist only in certain of these life zones and we need not expect to find them elsewhere. Russian thistle grows in eastern Washington and Oregon because this is its proper life zone but cannot grow in western Washington and Oregon, west of the Cascade Mountains, on the coastal plain, because this is not its life zone. Velvet grass exists as a chief cause of pollinosis in the latter area but is not found in the former for the same reason. Ragweed flourishes east of the Rocky Mountains but has not passed the barrier of a different life zone in the higher altitudes farther west. Indeed, it is doubtful whether it would succeed in establishing itself on the Pacific Coast even if it did pass this barrier, unless it could adjust itself to a new cycle in its growing period. Ragweed requires abundant rainfall in June, July and August which does not exist in California. There, the rainy period is in November, December, and January.

The weather and pollen seasons.—Aside from floral distribution, weather always plays a part in pollen distribution and prevalence, especially so with wind-pollinated plants. Weather influences pollen in two very general ways: (1) the time of onset of flowering and profuseness of vegetation; and (2) once this has been established, the amount of pollen that is to be distributed into the air from day to day.

There are three major pollen seasons of interest to allergists, the early spring season representing pollination of trees; the late spring or early summer season due principally to the grasses; and the late summer and early fall season due chiefly to weeds. The time of onset of the first is variable, the second rather less so, while the onset of the third is remarkably constant, usually varying by no more than a few days from year to year.

The severity and duration of the winter control in great measure the onset of tree pollination. In Virginia trees commence pollination early in February. Farther north or south the usual date varies by periods up to two weeks or more. Following an unusually short, warm winter I have seen maple, elm and alder bloom early in January, June grass which usually pollinates early in May, has bloomed in January. An unusually long winter will postpone the dates accordingly. There is usually less variation in the flowering of grasses than of trees. On the other hand, plants which bloom in late summer are quite uninfluenced by the duration of the winter. The one preseasonal factor of greatest importance for them is rainfall. This rarely influences the date of pollination but does very materially influence the profuseness of vegetation. The abundance of a ragweed crop is predetermined chiefly by the abundance of rainfall in June, July and early August. A drought at this time usually augurs a mild hay fever season; abundant rainfall the reverse.

Ragweed pollination in Virginia usually commences around the tenth of August, with significant amounts of pollen grains appearing in the air by the eighteenth. In 1930 a drought lasted through the summer until August 27, when there was a severe storm during which two inches of water was precipitated. The pollen season was delayed by the drought, but within four days after the heavy rainfall normal amounts of pollen for that time appeared in the air. Thereafter, prevalences ran about the average for other years. This

was an unusual situation in which a drought extending into the first part of the period did influence the date of onset.

Once the flowering period has commenced, weather conditions no longer predetermine the amount of potential pollen in the plant, to be distributed

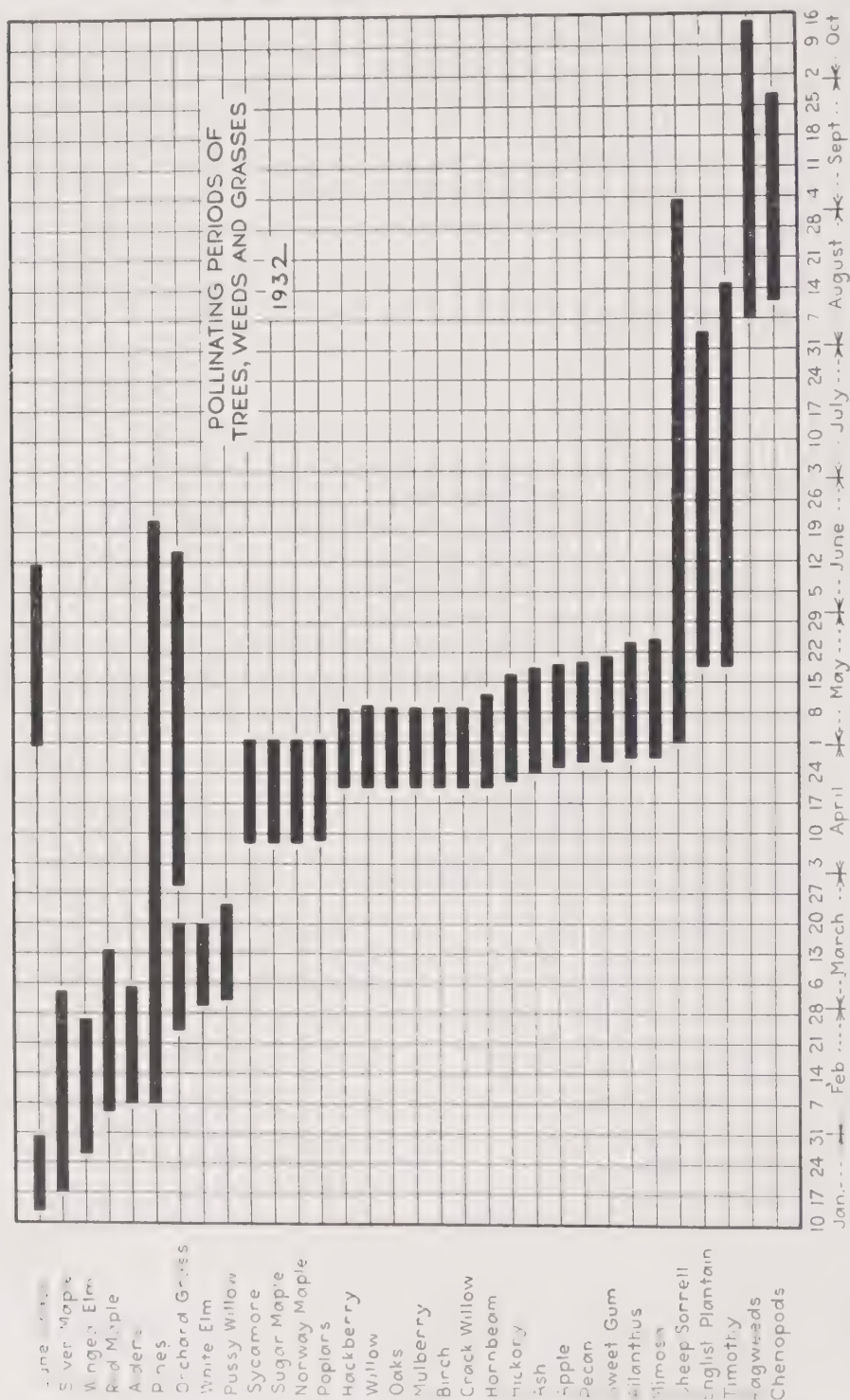


Fig. 97. Results of field survey. Examination for active pollination at the source of supply. This differs from pollen counts at the point of delivery (pollen slide, patient's nose). The effect of an open winter in Virginia is indicated by early pollination of June grass, maple, and elm in January. A heavy frost late in January terminated grass pollination which terminated at about the usual time in May. In 1932 the tree season was advanced by about two weeks. Note that some ragweed was flowering August 7, although not enough was delivered into the air to be of importance in pollinosis until August 18. (From Vaughan, "Allergy and Applied Immunology," Second Edition, St. Louis, 1934, The C. V. Mosby Company.)

into the air but, rather, determine in great measure the amount which will be distributed from the plant, into the air from day to day.

Durham states that the ideal conditions for heaviest ragweed plant production are an average summer temperature of 70° to 80° F., and a total

spring and summer rainfall of from 10 to 35 inches. Ideal conditions for maximum pollen ripening and transport are very sunny weather with occasional rains only at night, high winds, low humidity, with a temperature of not less than 50 degrees.

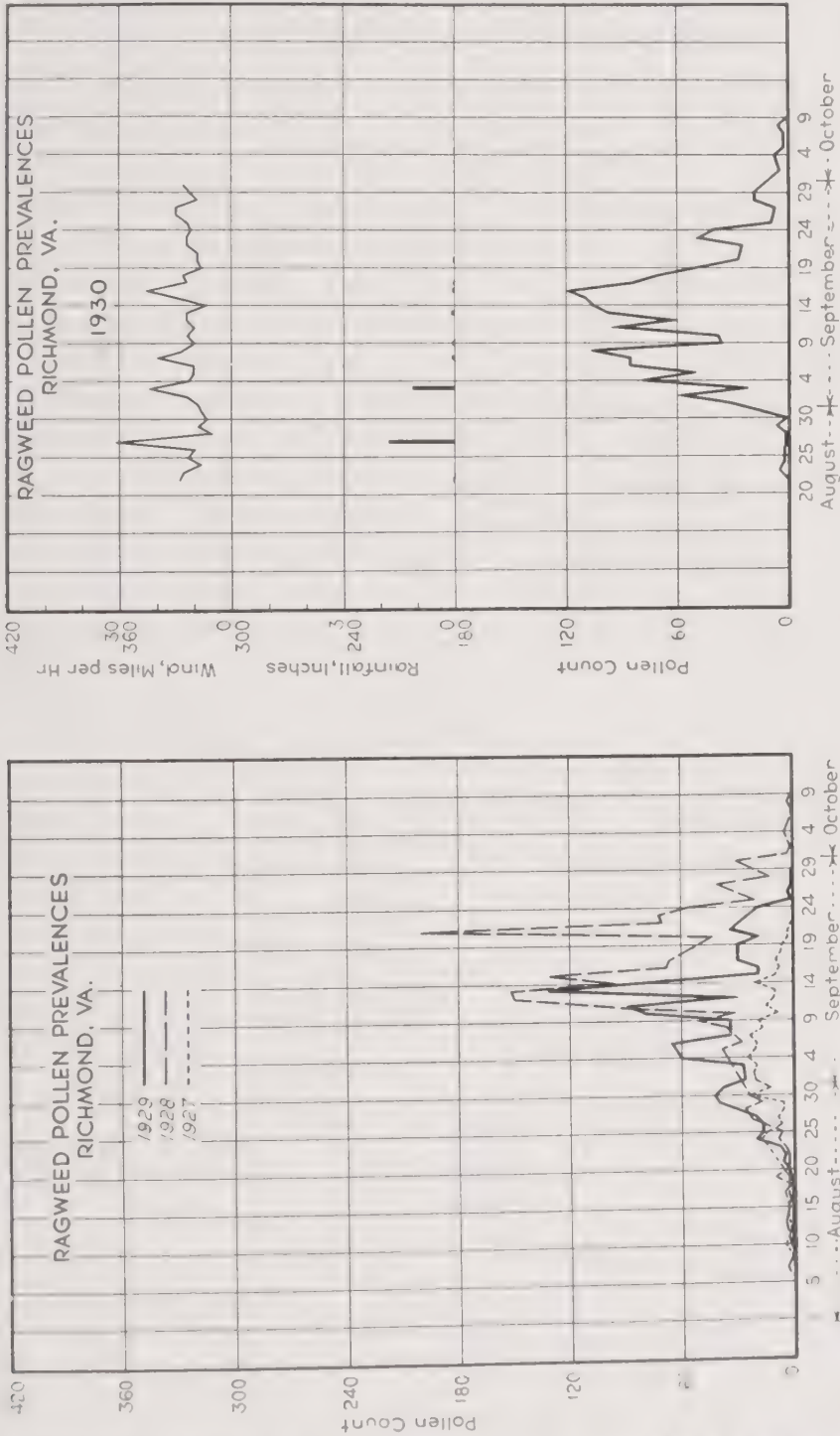


Fig. 98.—Ragweed pollen prevalences in Richmond, 1927 to 1930, inclusive. Note the distinct variation in the first three years and the lag in date of onset to August 31, in 1930. This was a drought summer and there was little pollen in the air until after a heavy storm with two-inch rainfall on August 27. Once started, pollen prevalence was fairly heavy. The peak of prevalence was not delayed, coming as usual around mid-September. (From Vaughan, "Allergy and Applied Immunology," Second Edition, St. Louis, 1934, The C. V. Mosby Company.)

Sunshine. Plants do not deliver pollen into the air at a constant rate, with no variation day or night. The major amount is released during certain periods of the day. This varies with different plants, some shedding in the afternoon, but more in the morning. Ragweed delivers most of its pollen

in the morning. It is stimulated to this in great measure by sunlight. Much more pollen is delivered on a sunny than on a cloudy day. Almost as much is released if the morning is sunny, even though the afternoon be cloudy. Conversely, if the morning is cloudy, much less pollen is liberated even though

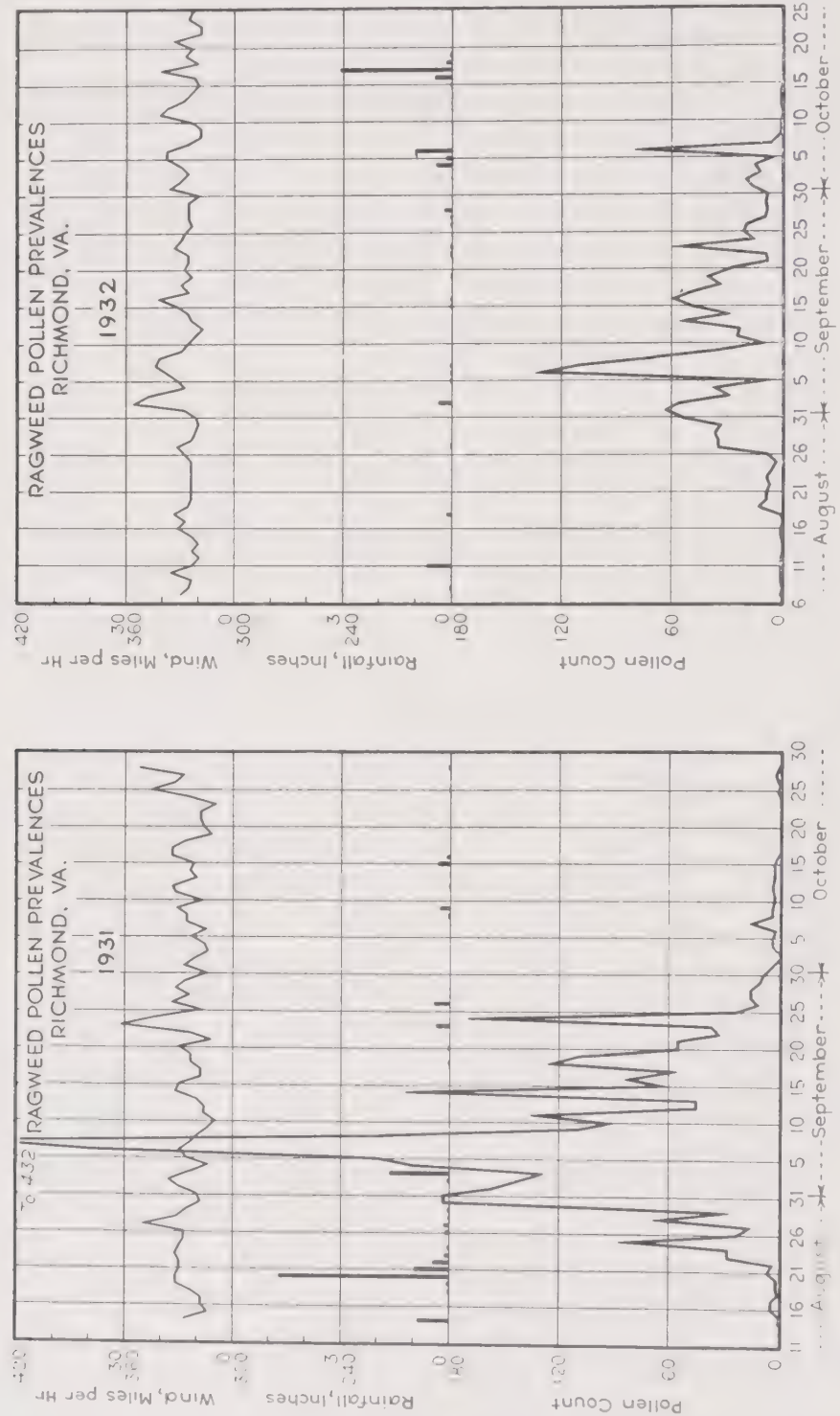


Fig. 99.—Ragweed curve showing the effect of weather, wind, and rainfall. The 1931 peak followed a week of stormy weather with somewhat increased wind velocity. The peak of Sept. 24, 1931, followed a wind storm. There was a similar peak late in the next season, Oct. 5, 1932, due to similar causes. On Oct. 17, 1932, the activity of these same factors caused no peak, because pollination had terminated. There was as yet no frost. The common statement that hay fever is terminated at the first frost is based chiefly on coincidence. (From Vaughan, "Allergy and Applied Immunology.")

the afternoon be bright and sunny. Early morning rainfall or high humidity prevents the plants from opening and discharging their pollen. The 1937 ragweed season in Virginia was preceded by a heavy rainy season. Consequently, plants were abundant, and well developed. The situ-

ation was rather the opposite of that for 1930, described above. We anticipated a heavy hay fever season. Instead, it was much lighter than usual. This is explained by the continuance of cloudy weather through the pollen season. Although the sun shone rather frequently in the afternoon, it rarely did so for long in the mornings.

It is usually stated that Bermuda grass pollinates at sunup. Knapp* states that it pollinates at sundown and continues to do so through the night. As a rule it has been seen pollinating in the early morning but few people have occasion to observe it during the night. This night pollination might be one factor accounting for pollinosis cases being worse when in the night air.

Wind and storm.—A heavy wind stirs more pollen into the air and carries it farther. Storms, even with rain, accompanied by high winds are often also accompanied by "epidemics of hay fever." The wind blows an abundance of pollen into the house where it is not washed out by the rain.

We have mentioned pollen clouds in which the grains are kept high by wind currents. In absolutely still air, ragweed pollen falls at a rate of about 10 feet per minute; but with a wind velocity of 6 miles per hour, it will require nearly three hours for settling out.

On warm days there is an upward convection current which carries the pollen about a mile in the air to form a pollen cloud. The cooler, falling current of the evening brings the pollen toward the earth. This may be one reason why hay fever patients experience more severe symptoms in the late evening and after midnight.

The direction of the prevailing wind is sometimes of importance. An on-shore wind in any coastal area will carry less pollen than an off-shore wind. Durham finds this also true for smaller bodies of water. In Chicago and Cleveland, for example, persons have less severe symptoms when the wind blows from the direction of the lake. In Canada, northwest winds from the forest area are beneficial while those from the south and west which have traversed agricultural sections usually carry heavy doses of pollen. Careful study of the weather map which is available for all sections, often published in the daily papers, will be of aid to the allergist. He may thus know from day to day the probability of heavy and light periods during the season. Areas of high and low barometric pressure, general wind direction and predictions concerning cloudiness and rain in neighboring sections of the country will often enable the allergist to predetermine whether he will have a busy day. Merely reading the daily newspaper weather forecast helps materially. The allergist will do well to arrange with the nearby weather bureau to receive the regular monthly weather summary for study at the end of the season. He can thus compare meteorologic factors with the daily fluctuations of his own recorded pollen counts.†

Hay Fever Pollen

In the preceding pages we have discussed the nature and characteristics of pollen, and factors influencing its distribution into the air. Not all pollens,

*Knapp, J. Smith: Personal Communication.

†A physician strongly allergic to ragweed drove in September, 1936, from Richmond to Colorado Springs, at the height of the ragweed season. He had had no preseasonal treatment. He took a protective face mask with him and found that he could wear it for an hour, and leave it off for two or three hours. The surprising part was that he had practically no trouble even though he went through the Mississippi basin where ragweed concentration is usually high. In this particular year there had been a drought. There was therefore only a small ragweed crop, and a plague of grasshoppers had eaten much of this. Contrary to expectation, therefore, the ragweed pollen prevalence was low.

not even all air-borne pollens, cause hay fever. Fortunately, the number of hay-fever-causing pollens is small as compared with the total potential number.

Thommen's five postulates.—Thommen has enumerated five postulates which must be fulfilled before a pollen can cause epidemic or endemic pollinosis.

1. The pollen must contain an excitant of hay fever.
2. The pollen must be anemophilous.
3. It must be produced in sufficiently large quantities.
4. It must be sufficiently buoyant to be carried considerable distances.
5. The plant producing the pollen must be widely and abundantly distributed.

These postulates apply to epidemic or endemic hay fever, obviously not sporadic hay fever, as in gardeners, florists, etc. As with most postulates there are exceptions, but the exceptions usually deal with the individual rather than with large groups.

With the increase in our knowledge of the biology of plants whose pollen is airborne, it becomes possible to say with assurance what ones are important to the allergist and which ones are not; which ones will assume increasing importance in certain parts of the country; which may become more or less important because of changes in the population or the cultivation of the land or even changes in farming practices. The influence of weather conditions upon plant growth and pollen production and distribution is now better understood.

If the presently accepted theory of the production of allergic symptoms by histamine is correct, then it becomes necessary to abandon the concept of the toxicity of pollen and to recognize that the severity of symptoms is due rather to the amount of pollen reaching the respiratory mucosa and its absorption. The severity of symptoms probably is related quantitatively to histamine production. Everyone has had the experience of working with a pollen extract which produced local reactions with minute doses and caused systemic reactions unless administered with great care. These are usually considered "toxic" pollens. The "toxicity" probably is dependent upon the amount of antigenic material which goes into solution, or the amount of antibody which it stimulates. It certainly is not due to a toxic fraction preformed in the pollen grain.

CHAPTER XLII

AEROBIOLOGY: DEVELOPMENT AND TECHNIC

By

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One should know not only what air-borne pollens are being produced in the field, but which of them are being carried in the air in appreciable quantities at places remote from their sources. While field inspection of the botanic sources of atmospheric contamination affords considerable information about the distribution of plants, as well as their productive ability and season of pollination, the results of even the most carefully planned field studies are not entirely adequate for the purposes of the allergist. At best they are not quantitative—not statistical—and do not afford any information whatsoever about the vertical or lateral range of the aerial dissemination of the actual offending allergens. A more direct approach to the basic problem of quantitative contact of the sensitive membranes of allergic persons with air-borne pollens and fungus spores of particular genera and species is that furnished by aerobiology, which has been defined as “the study of the aerial carriage of microscopic objects,” aero-micro-biology.

The essential contribution of aerobiology to allergy is that of determining with reasonable accuracy the relative and actual *amounts* of aero-allergens that may be contacted in any *place* at any *time*. Obviously the aerobiologist assumes a share of the task of discovering and evaluating new aero-allergens. Incidentally, he must also be able to account for certain phases of the aerial behavior as well as the distribution of pollens and similar allergens.

A census of aerial populations would be a very simple matter if all of the microscopic particles were spherical in shape, of uniform weight, volume, and surface character, and if they were held in permanent suspension and in uniform distribution in perfectly still air. But, in actual practice, the concentration of pollen grains and similar allergens in outdoor air varies greatly from season to season, from day to day, and even from hour to hour. Obviously, it also varies greatly from place to place. The particles themselves differ considerably in size, density, and surface texture, except for a reasonable uniformity among the pollen grains or spores of a given species. Instead of being suspended in still air, they are constantly being moved about laterally and vertically by the wind, by convection currents, and by gravity, and the latter pulls the larger ones down faster than it does the smaller ones. This makes it necessary to do extensive testing at different times of day every day in the year, in various places, and even at different levels in the upper air. At best we can obtain only an approximate picture of the actual exposure of a given individual who necessarily moves from place to place in the course of a day's activities.

Air Sampling Methods. Quantitative aerial samples of pollen or other air-borne allergens may be secured by washing or filtering the particles from a known volume of air, or by impinging them on ordinary glass microscope slides which have been coated with a thin film of petrolatum or other suitable adhesive. Much effort has been spent on perfecting air filters and scrubbing devices, but

none of the instruments so far offered has been widely used. Seldom has any of them been used in routine aero-allergen surveys, because of the expense involved in their manufacture, and because of the time consumed in their operation or in counting the samples.

For their studies on the atmospheric incidence of apple scab spores, Keitt and Jones (1926) developed a filter which consisted essentially of a vacuum pump which pulled air through a nitrocellulose filter at the rate of about 60 cubic feet per hour. An instrument of the same design has been used for control purposes by the author of this chapter in a short series of aero-allergen tests. The rather tedious technic of counting is described in the second paper of his

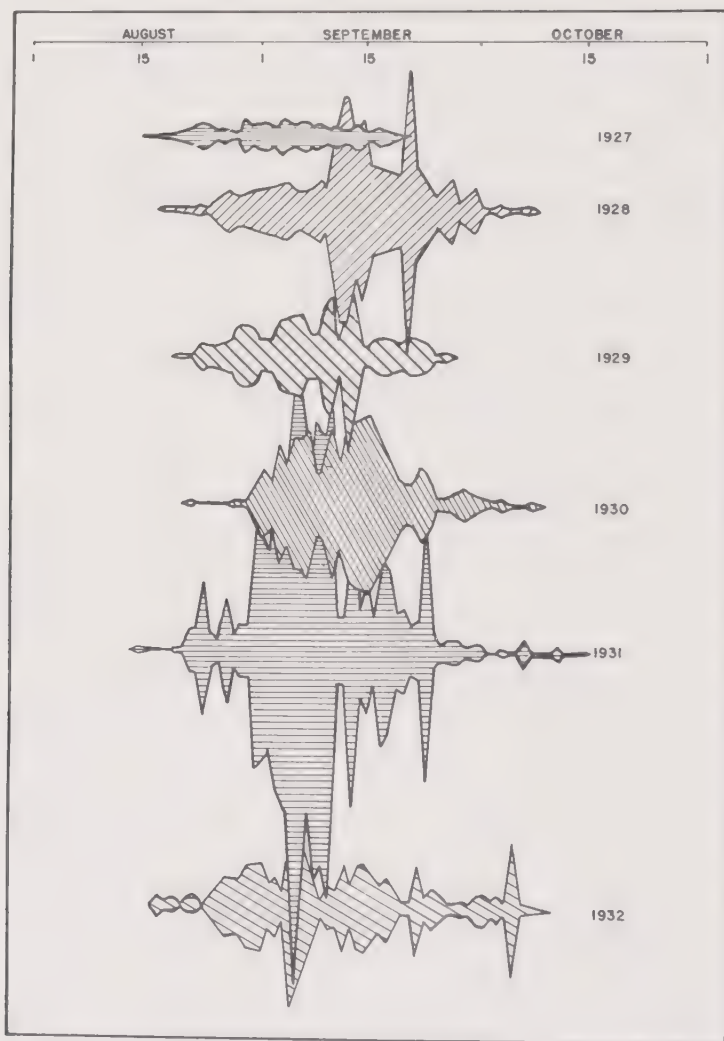


Fig. 100.—Ragweed pollen incidence in Richmond for eleven successive years. In general, pollen abundance depends on favorable climatic conditions during the growing period; individual daily peaks depend on weather conditions from day to day during the period of flowering. No two seasons are identical and good results with speed treatment during any given season cannot be accurately evaluated without some knowledge of the comparative severity of the particular season. Keeping such charts on a blackboard from day to day during the season enables the patient to understand a possible flare-up in symptoms on any given day, when pollen prevalence happens to be unusually high.

monograph entitled "The Volumetric Incidence of Atmospheric Allergens" (1944). Erdtman (1938) tested the air over the Atlantic Ocean during a trans-oceanic voyage by means of a vacuum cleaner using paper filters. The apparatus drew approximately 200 cubic meters of air per hour. As set up for ocean tests, it would not be adapted to pollen research on land, except perhaps for limited spot testing.

The impingement of particles on an adhesive surface may be accomplished by very simple devices. Samples obtained by these devices are also easily inspected and counted. Some of the available forces which have been used for impingement include: centrifugal force, natural wind currents, electric fan currents, suction currents produced by vacuum pumps, and rapid movement of the adhesive-coated slide against the air. While impinger sampling devices are much simpler to build and to operate, they are likely to yield less accurate results than air filters. The ultimate in simplicity is found in the gravity slide technic in which an adhesive-coated slide is exposed in a horizontal position for twenty-four hours. This is the method which has been used in securing nearly all of the extensive statistics which have been gathered during the last three decades, particularly the last two.

Several attempts have been made to use and perfect the impinging methods noted above.⁴ Mostly they have been without success. Penfound and Efron (1930), noticing the great discrepancy in the gravity counts obtained in various situations on the same day and by slides set at different angles in the same location, suggested the adoption of a standard sampling device which consisted of a weather vane carrying one horizontal slide and another slide vertically facing the wind. They concluded that the catch on the vertical slide gave the more accurate measure of the air content, particularly on days of high wind velocity, but for this they submitted no proof. Nor did they outline a standard counting technic that would correlate the data from both the vertical and horizontal exposures. Phillips (1941) used a modified form of the Penfound and Efron apparatus in making a pollen survey in Australia. Air sampling by means of wind impingement on vertically exposed slides is mentioned only to be condemned. The method introduces an unnecessary variable factor, wind velocity, into a process which at best is plagued with variables.

Duke (1932), who was also dissatisfied with gravity sampling, proposed the use of a motor-driven hair drier which delivered a stream of air of constant velocity and thus afforded an ideal means for impingement of allergens from the air. The device was never used in a routine survey. The outstanding objection to this sampling method is the lack of volumetric control. Resulting data could be only relative unless the instrument were calibrated against a reliable volumetric sampling device. A limited amount of pollen sampling has been done with the Wells centrifuge, but the resulting data have not been published.

The writer (1947) has described a vacuum hand pump which impinges the contents of the air in three small spots on an oiled slide (capacity $4\frac{1}{2}$ cubic inches per stroke), also an air "whip." Both instruments are useful for making spot tests for immediate readings. The latter instrument is a shaft 36 inches long by which a prepared slide may be whirled in the air face forward at an approximate rate of 50 miles an hour. When the instrument is calibrated against a volumetric filter, it can be used for making fairly accurate tests of the aero-allergen content of the air.

In making tests of pollen and spore concentrations in the upper air, from ground level to the ceiling of such particles, ordinary sampling methods cannot be used. To obtain samples from a moving airplane it has been found sufficient to place an oiled slide in the slipstream for a very short time. The author has adopted a unit for exposure outside the cockpit of 5 air miles. The results of such tests give only relative figures since no way has been found of translating them into volumetric equivalents.

Development of a Standard Gravity Technic.—An ideal plan for a standard gravity technic must cover at least the following points:

1. A sampling device, otherwise known as a slide exposure shelter, which will not only protect the slide from the heavy wash of rain, but will be free from air baffles of any sort that might cause undue deposit of air-borne particles.
2. A definite slide area to be counted.
3. A simple comprehensible method of stating the statistical results, preferably on the basis of the number of pollen grains (or other aero-allergens) found in a unit volume of air.

The approach to this goal has been very uncertain, not because of any difficulty that could have been encountered in adopting a standard shelter and a standard counting area, but because of the technical difficulties involved in interpolation of gravity data. The Committee on Aerobiology of the National Research Council which was organized in 1938 by a group of plant pathologists and allergists has recognized the need of standard practices in the allergy field and set up committees to work toward that end. Nevertheless, progress has been slow.

Charles Harrison Blackley (1873) was the first allergist to take an active interest in the atmospheric dissemination of pollen grains and fungus spores. As early as 1856 he carried out systematic air tests during the season of grass pollination at Manchester, England. His early efforts had been directed toward perfecting a volumetric sampling device, but after failing in this he made extensive use of the gravity slide method. His exposure device was pictured and carefully described. His counting unit was 1 square centimeter. He did not attempt volumetric interpretation of his figures. At the suggestion of Dr. Blackley, an American physician, Dr. Elias J. Marsh, made a few gravity slide tests in New York City and in Paterson, New Jersey, during the ragweed season of 1875.

A single premature attempt to apply the pollen counting methods of Blackley was made in 1888 by Professor Samuel Lockwood of Freehold, New Jersey, who, because of his own hay fever, was accustomed to spending his summers at Bethlehem, New Hampshire. During the season of 1889 he exposed two series of daily pollen slides, one in his home town in New Jersey, and one at Bethlehem. The exact results of this study have not been preserved, but the report states that large quantities of ragweed pollen were found on the slides at Freehold and none at all at Bethlehem. Unfortunately, the study was not continued because the hotel keepers in the White Mountains refused to furnish funds for such research.

No further aerobiologic research was attempted until 1916 when Dr. William Scheppegegrell began his local sampling and counting in New Orleans. His results were not reported until 1923. In this work he used the gravity method of sampling, but failed to describe his sampling device. He counted 1 square centimeter of slide area as Blackley did. Preferring to state his results in absolute terms, he attempted, by an application of Stokes' law for small falling bodies, to derive a formula by which the number of pollens found on a square centimeter could be changed directly into volumetric equivalents (number per cubic yard of air). Unfortunately, he did not take into consideration several important factors affecting the gravity deposit of pollen grains, nor did he submit his theoretical conclusion to any sort of control test. If he had he would have caught the mathematical errors in the calculations made for him by a collaborator. Twenty years elapsed before attention was called to them. Mean

while the Scheppegrell table of conversion factors was widely publicized, though not unanimously adopted. Most of the pollen data published during these two decades—whether from local studies or from coordinated nationwide surveys (Durham, 1937)—were stated as “the number of pollen grains found on an area of 1.8 square centimeter (or 1 square centimeter) of slides exposed in a horizontal position for twenty-four hours.” In one survey, Deamer and McMinn (1935), the data were reported in “pollens per square foot.” However, this unit was adopted merely for purposes of statement. The counting had been done on an area of 1 square centimeter, and the findings in every case multiplied by one thousand.

The mathematical errors in the Scheppegrell table of conversion factors were finally corrected by Cocke (1937), who also carried out a short series of parallel volumetric-gravity tests (1938) which seem to prove that his own revised factors were essentially correct—that pollen grains in outdoor air fall at the same rate as they would in still air, regardless of wind currents. A few years later Hawes, with co-workers (1942), reported from Los Angeles a comparative volumetric-gravity study similar to that made by Cocke. In this study he used a volumetric impinger apparatus which samples approximately 5 cubic feet of air per hour.

Rate of Fall and Specific Gravity Studies.—

Not being satisfied with the proof offered by either Cocke or Hawes, and encouraged by Dahl's (1942) clear presentation of the unsolved problems of pollen aerobiology, the author of this chapter began in 1942 a series of comprehensive studies on the volumetric incidence of atmospheric allergens. The first step in the inquiry was to determine the specific gravity of pollen grains of a number of species which are important in allergy. The result showed that errors of a magnitude of 100 per cent had been introduced into the conversion factors recommended by Scheppegrell, Cocke, and Hawes, all of whom had assumed that all pollen grains have a specific gravity of 1.0. The second step consisted of testing the rate of fall of pollen grains in still air. A total of thirty-eight pollen species were tested. In this experimental study it was found that pollen grains of all the common hay fever plants, except the ragweeds and Russian thistle, fall slower than the calculated rate, when their specific gravity is given full consideration. In general, they obey Stokes' law, the larger ones falling faster than the smaller ones. Even so, it still remained to determine the actual performance of pollen grains in *outdoor* air where the effect of gravity is seriously modified by the stronger forces of lateral wind currents and air turbulence.

The volumetric impinging sampling device which had been used by Hawes in California was placed at the disposal of the author and was used by him for four seasons in making parallel volumetric-gravity tests of the pollen and fungus spore content of the air in North Chicago. The location chosen for carrying out the sampling was the flat roof, 182 by 65 feet, of a warehouse at Abbott Laboratories. This building was higher than any surrounding building (55 feet above the ground) with the roof unobstructed except for two small penthouses.

Simultaneous gravity slide exposures and volumetric runs with the Hawes device were made thirty-nine times during the late summer and fall of 1942 and eight times during August, 1943. The gravity slides were coated with a very thin film of petrolatum, no label being used, and were exposed face up on the end of a vertical 22-inch rod placed several feet from the volumetric apparatus. Hawes had suggested this as an ideal sampling method, although he had not used it himself.

TABLE XXXI. ORIGINAL DATA ON SPECIFIC GRAVITY AND RATES OF FALL

COMMON NAME	BOTANICAL NAME	DI-AMETER IN MICRONS*	SPE-CIFIC GRAV-ITY†	RATE OF FALL IN FEET PER SECOND		EXPERI-MENTAL RATE AS COMPARED WITH SHORT RAGWEED
				CALCULATED	EXPERI-MENTAL	
Giant ragweed	<i>Ambrosia trifida</i>	19.25	0.52	0.019	0.027	0.93
Burweed marsh elder	<i>Iva xanthifolia</i>	19.3	0.79	0.029	0.031	1.07
Short ragweed	<i>Ambrosia elatior</i>	20.0	0.55	0.022	0.029	1.00
False ragweed	<i>Franseria acanthicarpa</i>	22.0	0.75	0.036	0.033	1.14
Marsh elder	<i>Iva ciliata</i>	23.0	0.58	0.031	0.039	1.34
Southern ragweed	<i>Ambrosia bidentata</i>	23.0	0.50	0.026	0.038	1.31
Western ragweed	<i>Ambrosia psilostachya</i>	26.4	0.57	0.039	0.046	1.59
Cocklebur	<i>Xanthium commune</i>	27.0	0.45	0.032	0.045	1.55
Russian thistle	<i>Salsola pestifer</i>	23.6	0.90	0.050	0.061	2.10
Palmer's amaranth	<i>Amaranthus palmeri</i>	25.8	1.02	0.067	0.061	2.10
Western water hemp	<i>Aenida tamariscina</i>	27.5	1.01	0.076	0.048	1.66
Mexican fireweed	<i>Kochia scoparia</i>	32.7	0.97	0.104	0.094	3.24
Annual sage	<i>Artemisia annua</i>	20.4	1.02	0.042	0.033	1.14
Tall wormwood	<i>Artemisia caudata</i>	21.0	1.04	0.046	0.032	1.10
Sagebrush	<i>Artemisia tridentata</i>	25.85	1.03	0.068	0.052‡	1.79
Nettle	<i>Urtica gracilis</i>	14.0	0.77	0.013	0.011‡	0.38
Red sorrel	<i>Rumex acetosella</i>	21.45	0.78	0.036	0.031	1.06
Hemp	<i>Cannabis sativa</i>	25.0	0.82	0.051	0.034	1.17
English plantain	<i>Plantago lanceolata</i>	27.5	0.97	0.073	0.049	1.69
Bluegrass	<i>Poa pratensis</i>	28.0	0.90	0.070	0.048	1.66
Bluegrass	<i>Poa pratensis</i>	30.0	0.90	0.080	0.057	1.97
Bermuda grass	<i>Capriola dactylon</i>	28.5	1.01	0.082	0.061	2.10
Orchard grass	<i>Dactylis glomerata</i>	34.0	0.91	0.105	0.091	3.14
Timothy	<i>Phleum pratense</i>	34.0	0.90	0.104	0.092	3.17
Rye	<i>Secale cereale</i>	49.5§	0.98	0.238	0.141	4.86
Corn	<i>Zea mays</i>	90.0	1.00	0.804	0.600	20.7
Sycamore	<i>Platanus occidentalis</i>	22.22	0.92	0.045	0.034	1.18
Mountain cedar	<i>Juniperus sabinoides</i>	22.8	1.08	0.056	0.038	1.31
Hazelnut	<i>Corylus americana</i>	23.6	1.09	0.060	0.043	1.48
Birch	<i>Betula nigra</i>	24.6	0.94	0.056	0.055	1.90
Alder	<i>Alnus glutinosa</i>	26.0	0.97	0.065	0.048	1.66
Ash	<i>Frazinus americana</i>	27.1	0.90	0.066	0.050	1.72
Cottonwood	<i>Populus virginiana</i>	30.0	0.79	0.070	0.050	1.72
Eln	<i>Ulmus americana</i>	31.2	1.00	0.097	0.067	2.31
Bur oak	<i>Quercus macrocarpa</i>	32.3	1.04	0.108	0.060	2.07
Shingle oak	<i>Quercus imbricaria</i>	33.1	1.04	0.112	0.072	2.48
Walnut	<i>Juglans nigra</i>	35.75	0.93	0.118	0.093	3.21
Beech	<i>Fagus grandifolia</i>	44.0	0.94	0.181	0.116	4.00
Hickory	<i>Carya ovata</i>	45.0	0.79	0.159	0.074	2.55
Scotch pine	<i>Pinus sylvestris</i>	52.0	0.45	—	0.082	2.82
Bull pine	<i>Pinus ponderosa</i>	60.0	0.45	—	0.115	3.95

*All measurements made on grains expanded in Calberla's solution.

†As determined by experimental methods described in the first paper of this series.

‡As calculated by performance of other similar granules.

§Mean of long and short diameters.

||Measured exclusive of wings.

Early in the 1942 season it was found that for no apparent cause the ratio between the gravity and volumetric catch of ragweed pollen from day to day varied enormously. In order to learn the source of these erratic results, it was decided to set up a second volumetric apparatus of entirely different design as a control on the first, and to operate both devices simultaneously with a gravity slide. The control apparatus finally adopted for the 1943 experiments was an air filter, patterned after that devised by Keitt and Jones. This control device delivered samples of ragweed pollen and *Alternaria* spores day after day which tallied remarkably well with those taken by the Hawes impinger, proving that most if not

all of the discrepancies were chargeable to inaccuracies of the gravity sampling method. In the ragweed tests the maximum divergence from the mean volumetric reading on any one day was only 20 per cent, and the average divergence less than 3 per cent.

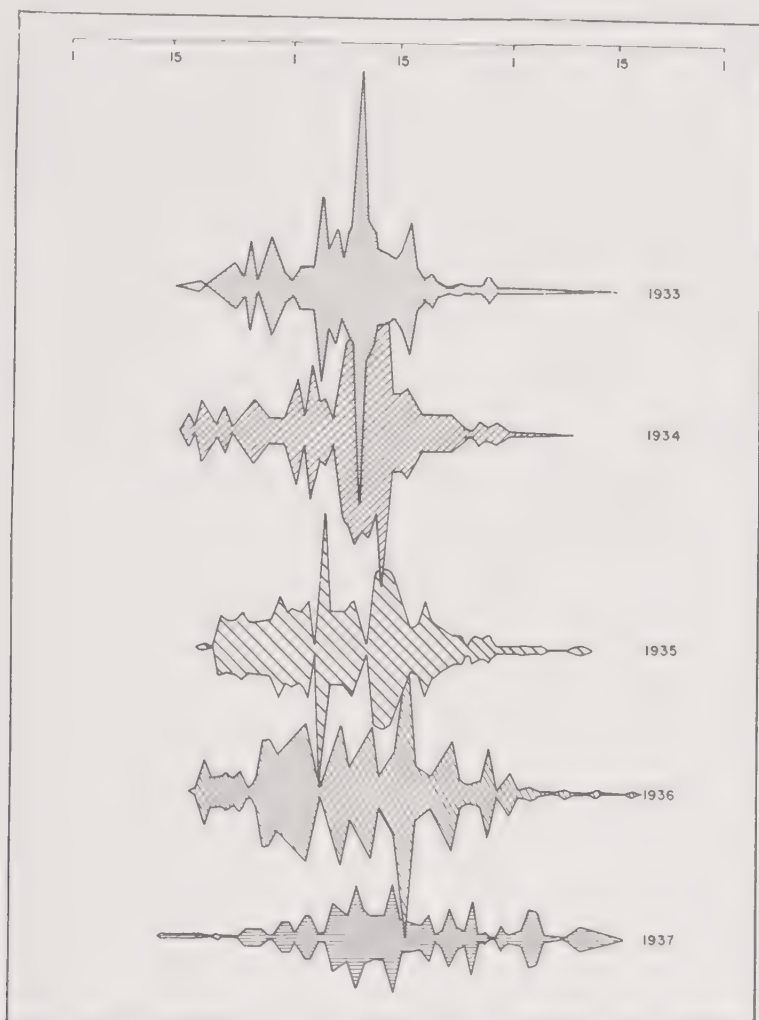


Fig. 101.—Ragweed pollen incidence in Richmond for eleven consecutive years (continued).

The data showed that in general, though not invariably, the proportionate catch of pollen on the gravity slides, as compared with that measured by the volumetric instruments, varied directly with the wind velocity. Since the largest excess amounts on the gravity slides tended to occur with the higher wind velocities, it seems reasonable to conclude that strong winds not only interfere with an even horizontal flow of air, but frequently act as an impinging force. To test this point, several slides were exposed in various positions in a 22-mile-per-hour wind. One was placed in the normal gravity slide position, another tipped at an angle of 45° to the wind, the third vertical facing the wind, the fourth slide tipped at an angle of 45° with the oiled face downward, and the fifth slide faced directly downward. The vertical and diagonal slides caught five to ten times as much ragweed pollen as the horizontal gravity slide, and the inverted horizontal slide actually caught 50 per cent as much as the normal gravity slide. It is thus evident that in strong winds there are upward as well as downward currents, and that wind impingement can, under such conditions, be responsible for most of the "gravity" catch.

Subsequent research with gravity slides exposed in various types of shelters has confirmed the results of our experience in exposing without shelter of any kind. We have had abundant proof that wind currents in the immediate vicinity of the slide can cause deposits of pollen and spores in almost every instance far in excess of those that can be accounted for by the effect of gravity. Thus, conversion factors based on Stokes' law are proved to be worthless, regardless of how carefully the formula may have been worked out. The only possible way to arrive at conversion factors that will have practical accuracy is to calibrate the actual average catch on slides exposed in a particular shelter with the catch in a reliable volumetric instrument operated simultaneously with the slide exposure.

Location of Sampling Station.—Since the greatest need for atmospheric pollen research is in the urban areas where the majority of the hay fever sufferers reside, it should be recognized at the outset that the "absolute pollen frequency of the air" differs widely at a given moment in various parts of any city and fluctuates greatly from hour to hour, as well as from day to day, in a given location. We must also recognize that buildings, trees and other objects cause unavoidable air turbulence and unpredictable air currents that greatly influence the deposit of pollen on gravity slides. Therefore, since no ideal testing location can possibly be found or arranged, the only type of location that can be regarded as *standard* for obtaining a typical daily average measure of city-wide air contamination is the top of a tall building in the downtown section—a point farthest from possible local sources of air pollution. The roof chosen should be level and, if possible, free from obstructions. If not, the spot on it chosen for exposures should be as far from obstructions as possible. When gravity tests are made in residence parts of the city the flat roof of an apartment building would be most likely to yield data comparable to those of a downtown location. Porches and window ledges are not recommended, but special and unusual locations may, of course, be suitable for the study of special local exposure problems. Certainly in reporting results of any atmospheric survey the sampling location should be stated and described or pictured in detail.

A Standard Gravity Sampling Device.—Until very recently little attention has been given to the slide shelter. In the nationwide sampling at weather stations for the author's coordinated studies the slides were usually exposed under the box which houses the Weather Bureau thermometers and other instruments. Acquarone and Gay (1931) pictured a slide shelter with a curved sheet metal roof, but gave no dimensions. Their design has been followed with considerable variation by several workers and has been recommended by Tuft (1938). This device is far from ideal because of its many air baffles which may cause a variety of wind currents, depending on differences in wind direction.

The device pictured in Fig. 102 makes use of two parallel planes of polished stainless steel held in position by three narrow struts. The purpose of these planes, aside from the rain protection afforded by the upper one, is to cause an even horizontal flow of air between them regardless of the direction or velocity of the wind. As used in the 1944 experiments, the oiled surface of the slide was held *flush* with the surface of the lower plane which was itself oiled in order to fix all pollen and other particles falling on it. In the form shown here and used for making comparative exposures during 1945, the slide holder is elevated 1 inch above the lower plane, thus allowing the air stream to flow underneath as well as over the slide. This has resulted in a smaller deposit of pollens and spores (as compared with our parallel volumetric determinations), thus more nearly approaching the ideal calculated gravity deposit.



Fig. 102.—Standard air-sampling device. The apparatus consists essentially of two parallel planes of polished stainless steel, 9 inches in diameter, with the slide holder raised 1 inch above the lower plane. It is supported by a 30-inch metal rod on a tripod laboratory stand. Screw holes are provided in the base so that it may be fastened securely to any wooden floor. (From *Journal of Allergy* 17: 81, March, 1946.)

Calibration of Sampling Device.—A series of seventeen tests (approximately one hundred thirty-six hours) were carried out using the gravity sampling device in parallel with the Hawes impinger during the ragweed season of 1945 (Table XXXII). Part of the tests were made on the roof of a three-story research laboratory building in North Chicago, and part on the seven-story annex of the post-office building in Milwaukee. While air samples of ragweed, taken with the device, contained on the average nearly three times as much pollen as

TABLE XXXII. EXPERIMENTAL RATING OF STANDARD SAMPLING DEVICE

PLACE	DATE 1945	GRAVITY: POLLENS PER SQ. CM. IN 24 HR.	VOLUMETRIC: POLLENS PER CU. YD. OF AIR, AVERAGE	RATIO GRAVITY/ VOLUME
North Chicago	August 20	34	110	3.2
North Chicago	August 24	100	254	2.5
North Chicago	August 26	9	10	1.1
North Chicago	August 27	169	273	1.6
North Chicago	August 28	111	681	6.1
Milwaukee	August 30	47	180	3.8
Milwaukee	August 31	222	821	3.7
Milwaukee	September 2	57	130	2.3
Milwaukee	September 3	52	115	2.2
North Chicago	September 5	66	407	6.2
North Chicago	September 6	30	202	6.7
North Chicago	September 7	113	159	1.4
North Chicago	September 9	68	478	7.0
North Chicago	September 10	45	201	4.4
North Chicago	September 11	45	183	4.1
North Chicago	September 12	16	38	2.4
North Chicago	September 19	10	55	5.5
Totals		1,194	4,297	
Ratio of totals				3.6

would be predicted by Stokes' law (using my experimental rate of fall for short ragweed for purposes of calculation), the daily figures were more consistent in their relation to the daily volumetric ragweed pollen determinations than those obtained with uncovered slides, and much more consistent than those from gravity slides exposed by the old Weather Bureau method. The volumetric control tests made in parallel with each gravity test showed an average of 3.6 times as many ragweed pollen grains per cubic yard of air as were deposited on 1 square centimeter of the gravity slides exposed for twenty-four hours. (For shorter exposure periods than twenty-four hours a larger equivalent area was counted.)

Standard Conversion Factors. The factor—3.6—has been adopted by the National Pollen Survey Committee of the American Academy of Allergy. It is to be regarded for present purposes as a standard conversion factor for ragweed air sampling *with this instrument* in areas where short ragweed is predominant. Thus an approximation of the average *number of ragweed pollen grains per cubic yard of air* for a twenty-four-hour period may be obtained either by counting an area of 1 square centimeter on a twenty-four-hour slide and multiplying by 3.6, or by counting an area of 3.6 square centimeter. Since this latter area happens to be just twice the area that has been so widely used (1.8 square centimeter), this part of the counting and interpolation offers little difficulty.

The author suggests that this ragweed factor may be used as a pivot for establishing conversion factors for all other types of pollen found on slides exposed in the described standard apparatus. This can be done, as will be shown shortly, by means of the figures which have already been determined experimentally for the relative rates of fall of pollen grains of some forty other species of hay fever plants.

At this point an important question will naturally arise concerning the fact that a considerable part of the deposit on any slide is evidently caused by impingement rather than by gravity. How can we then apply rate of fall data as though all of the deposit were the result of the action of gravity? The answer is that inertia force acts in much the same way as gravity in sorting particles of different weights. The heavier particles in the air are impinged in greater proportion than the lighter particles, the latter tending to remain in the air and be carried around the edge of the slide which intercepts the air current. This has been verified a number of times by whirling an oil-coated slide through the air, oiled face forward, at a rate of approximately 50 miles per hour. Such a slide picks up a much smaller proportion of the lighter particles in the air, such as *Alternaria*, than of the heavier ragweed pollen grains as compared with the number of each in the air as shown by simultaneous volumetric sampling. Moreover, in the course of four seasons' experience with gravity sampling controlled with volumetric tests, it has been found that the more buoyant particles, such as nettle pollen grains and *Alternaria* spores, actually produce lighter "gravity" deposits than ragweed, while heavier pollen grains, such as Mexican fireweed, western water hemp, and hemp produce heavier deposits in about the expected proportion. Of course, the ideal procedure for setting up factors for oak, sagebrush, and hemp, as well as all other common air-borne pollens, is that followed for ragweed, but the work involved in making parallel volumetric-gravity tests under ideal conditions with statistical amounts of these pollens poses a task that will not be finished in many years. Therefore, for present purposes we must use factors derived indirectly as suggested above, basing calculations on rates of fall shown in Table XXXI and allowing for the same excess proportion of deposit in outdoor air as was found for ragweed.

It must be noted that these factors so derived as shown in Table XXXIII apply only to gravity slide data from exposures in the standard sampling device already described. Standardization of any other gravity sampling device which in the future may seem more acceptable than this one will require at least one season of daily volumetric control tests, preferably during a season of ample ragweed pollen incidence, and the development of a whole new set of conversion factors. In spite of variations in pollen grain size and specific gravity which necessarily affect the accuracy of the conversion factors here presented, it is quite likely that errors from these sources are much smaller than the inherent errors in any gravity sampling method. Extreme accuracy is an impossible goal in this field of research.

TABLE XXXIII. CONVERSION FACTORS FOR TYPICAL POLLENS

COMMON NAME	BOTANICAL NAME	DIAMETER IN MICRONS	EXPERIMENTAL RATE OF FALL	A	B
			AS COMPARED WITH SHORT RAGWEED	FACTOR FOR 1 SQ. CM.	FACTOR FOR 3.6 SQ. CM.
Giant ragweed	<i>Ambrosia trifida</i>	19.25	0.93	3.87	1.08
Burweed marsh elder	<i>Iva xanthifolia</i>	19.3	1.07	3.36	0.93
Short ragweed	<i>Ambrosia elatior</i>	20.0	1.00	3.60	1.00
False ragweed	<i>Franseria acanthicarpa</i>	22.0	1.14	3.16	0.88
Marsh elder	<i>Iva ciliata</i>	23.0	1.34	2.69	0.75
Southern ragweed	<i>Ambrosia bidentata</i>	23.0	1.31	2.75	0.76
Western ragweed	<i>Ambrosia psilostachya</i>	26.4	1.59	2.26	0.63
Cocklebur	<i>Xanthium commune</i>	27.0	1.55	2.32	0.65
Russian thistle	<i>Salsola pestifer</i>	23.6	2.10	1.71	0.48
Palmer's amaranth	<i>Amaranthus palmeri</i>	25.8	2.10	1.71	0.48
Western water hemp	<i>Acnida tamariscina</i>	27.5	1.66	2.17	0.60
Mexican fireweed	<i>Kochia scoparia</i>	32.7	3.24	1.11	0.31
Annual sage	<i>Artemisia annua</i>	20.4	1.14	3.16	0.88
Tall wormwood	<i>Artemisia caudata</i>	21.0	1.10	3.27	0.91
Sagebrush	<i>Artemisia tridentata</i>	25.85	1.79	2.01	0.56
Nettle	<i>Urtica gracilis</i>	14.0	0.38	9.47	2.63
Red sorrel	<i>Rumex acetosella</i>	21.45	1.06	3.40	0.94
Hemp	<i>Cannabis sativa</i>	25.0	1.17	3.08	0.85
English plantain	<i>Plantago lanceolata</i>	27.5	1.69	2.13	0.59
Bluegrass	<i>Poa pratensis</i>	28.0	1.66	2.17	0.60
Bluegrass	<i>Poa pratensis</i>	30.0	1.97	1.83	0.51
Bermuda grass	<i>Capriola dactylon</i>	28.5	2.10	1.71	0.48
Orchard grass	<i>Dactylis glomerata</i>	34.0	3.14	1.15	0.32
Timothy	<i>Phleum pratense</i>	34.0	3.17	1.14	0.32
Rye	<i>Secale cereale</i>	49.5	4.86	0.74	0.21
Corn	<i>Zea mays</i>	90.0	20.7	0.17	0.05
Sycamore	<i>Platanus occidentalis</i>	22.22	1.18	3.05	0.85
Mountain cedar	<i>Juniperus sabinoides</i>	22.8	1.31	2.75	0.76
Hazelnut	<i>Corylus americana</i>	23.6	1.48	2.43	0.68
Birch	<i>Betula nigra</i>	24.6	1.90	1.89	0.53
Alder	<i>Alnus glutinosa</i>	26.0	1.66	2.17	0.60
Ash	<i>Fraxinus americana</i>	27.1	1.72	2.09	0.58
Cottonwood	<i>Populus virginiana</i>	30.0	1.72	2.09	0.58
Elm	<i>Ulmus americana</i>	31.2	2.31	1.56	0.43
Bur oak	<i>Quercus macrocarpa</i>	32.3	2.07	1.74	0.48
Shingle oak	<i>Quercus imbricaria</i>	33.1	2.48	1.45	0.40
Walnut	<i>Juglans nigra</i>	35.75	3.21	1.12	0.31
Beech	<i>Fagus grandifolia</i>	44.0	4.00	0.90	0.25
Hickory	<i>Carya ovata</i>	45.0	2.55	1.41	0.39
Scotch pine	<i>Pinus sylvestris</i>	52.0	2.82	1.28	0.35
Bull pine	<i>Pinus ponderosa</i>	60.0	3.95	0.91	0.25

Formula for deriving factors in columns A and B:

$$\text{Factor A} = \frac{3.6}{\text{comparative rate of fall}} \quad \text{Factor B} = \frac{A}{3.6}$$

Factors are given for eight species of ragweed, six of which are of more or less restricted distribution. The amount of giant ragweed pollen in the air in most areas will hardly justify the use of a higher factor during the early part of the ragweed season. If in some areas the average size of air-borne ragweed pollen grains throughout the whole season or during the greater part of the season proves to be appreciably more or less than 20 microns, an adjusted factor should be used. The only other possible call for adjustment of the ragweed factor would be in the case of an experimenter finding the actual ratio of ragweed pollen per cubic yard of air to the number per square centimeter of slide at his place of sampling to be more or less than 3.6. Such a local factor could be established only by a long series of parallel volumetric-gravity tests.

The suggestions mentioned apply to the use of all other factors for the typical pollens listed in Table XXXIII. If, for example, the poplar pollen grains found on the slides in a particular locality average smaller or larger than the 30-micron cottonwood pollen which has been tested, a different local conversion factor will need to be calculated. This may be derived as follows, assuming that local poplar species measures 32 microns in polar diameter (expanded in Calberla's solution or other aqueous medium).

$$\frac{32^2}{30^2} = \frac{2.09}{x}, \text{ solving}$$

$$x = \frac{30^2 \times 2.09}{32^2} = 1.84$$

Obviously, no common factor can be used for grass pollens since the size of grass pollen granules varies considerably with the prevailing grass pollen in the air. The factor for redtop (diameter, 26 microns) will likely be about 2.8, and Canada bluegrass (diameter, 30 microns) about 1.97—as for bluegrass of that same diameter.

The set of factors in column A of Table XXXIII is to be used when the unit slide area counted is 1 square centimeter, but, in case it is deemed more convenient to count a slide area of 3.6 square centimeters, by which method ragweed figures will not need to be converted, the factors for other pollens will be found in column B.

Summary of Standard Gravity Technic

Essential Equipment.—

Standard sampling device as shown in Fig. 102. This apparatus can be purchased from Wilkens-Anderson Company, 111 North Canal Street, Chicago 6, Illinois. If the worker prefers to build his own instrument, a working drawing will be furnished without charge. Write to Matthew Walzer, M.D., 20 Plaza Street, Brooklyn 17, New York.

Compound microscope (preferably binocular) with mechanical stage (preferably with graduated scales and verniers).

Glass slides, 25 by 75 mm. (1 by 3 inches). If slides with frosted ends are used, no paper labels will be necessary.

Cover glasses, 22 by 22 millimeters.

Wooden slide boxes with covers, large size (twenty-five slides, for storing slides and small size (three slides) for carrying slides to and from laboratory and exposure site.

Soft petrolatum jelly: 75 per cent U. S. P. petrolatum, 25 per cent U. S. P. mineral oil.

Dissecting needle.

Calberla's solution, made up of 5 cc. of glycerin, 10 cc. of 95 per cent alcohol, 15 cc. of distilled water, and 2 drops of saturated aqueous solution of fuchsin. (Small tablets of basic fuchsin are prepared by Burroughs-Wellcome and Co.)

Specimen reference slides, photomicrographs, drawings of pollen grains.

Place and Time of Exposure.—The ideal location for the sampling apparatus is the center of an unobstructed roof of a tall, flat-topped building near the geographic center of a given community. The building chosen should not be immediately flanked by taller structures. If the roof is equipped with a parapet, the top of the exposure apparatus should be 30 inches above the parapet. Porches and window ledges are not satisfactory sites for pollen sampling.

Slides should be exposed, with label under the clip, for periods of twenty-four hours, starting preferably in the morning and at approximately the same hour each day.

Identification Technic.—Familiarity with the microscopic appearance of pollen grains can be gained only by actual study of pollen grains. While every worker should equip himself with the best obtainable photomicrographs and drawings, particularly with the descriptions and drawings of Wodehouse (1935, 1942, 1945), he cannot hope to attain facility in his work until he has built up his own personal library of reference samples obtained direct from the plants of the locality in which he works. These can be preserved in bulk form or can be mounted in any of several ways. The simplest possible library consists of oil-coated slides on which the various pollens have been dusted. These can be preserved in wooden boxes for many years without appreciable deterioration.

Slides should be prepared with a very thin film of petrolatum jelly (rubbed out—not flowed on with heat). Preparation of slides should be carried out in a room free from air currents and dust particles.

Examination of slides and identification of allergenic particles may be carried out most effectively by staining with Calberla's solution. The larger dirt particles, soot and sand should first be removed with a dissecting needle with the aid of a hand lens. A few drops of the stain are then placed directly on the slide. The amount used should be just sufficient to fill the space between the irregular oiled surface of the slide and the cover slip and will vary according to the quality of debris on the slide. If the cover glass actually floats free, the excess stain may be removed with a blotter. The slide may usually be examined within three to five minutes after application of the stain.

Identification and counting may be carried on without stain. Even when stain is used, only about one-half of the slide surface will be disturbed, leaving the remainder for observation of unstained granules.

The glycerin jelly method of slide preparation and counting as described by Wodehouse (1935) may be followed if preferred.

Counting.—For routine counting, low power should be used—usually a 10X objective with a 10X or 15X eyepiece. If no cover glass is used, a count is made of all pollen granules encountered in crossing the entire width of the slide (1 inch or 25 millimeters). The slide is then shifted laterally and another complete crossing is made. This is repeated until a standard area has been counted.

The area observed on one trip across a slide depends on the width of the low-power field afforded by the optical combination which is being used. The width of the field may be determined by reading the vernier setting of the stage, then shifting a given particle on the slide all the way from one side of the field to the

other and reading again. The shift will amount to 1 millimeter, more or less. A number of trials should be made and the results should be averaged. If the field width happens to be exactly 1 millimeter, then each trip across the slide will cover 25 square millimeters. Four trips will cover 1 square centimeter. If the cover glass technic is used, the count is made across the width of the cover glass (22 millimeters). If the optical field width is exactly one millimeter, each trip across the cover glass will cover 22 square millimeters, and five such counts will cover 110 square millimeters or 1.1 square centimeter. From this figure, the count for the standard unit of 1 square centimeter may be readily calculated. Or the whole area (4.84 square centimeters) under the cover may be counted by systematic sweeping of the cover glass area.

When there are only small amounts of pollen in the air, the accuracy of the results may be increased by counting an area of several square centimeters, and reducing the total to the average per square centimeter.

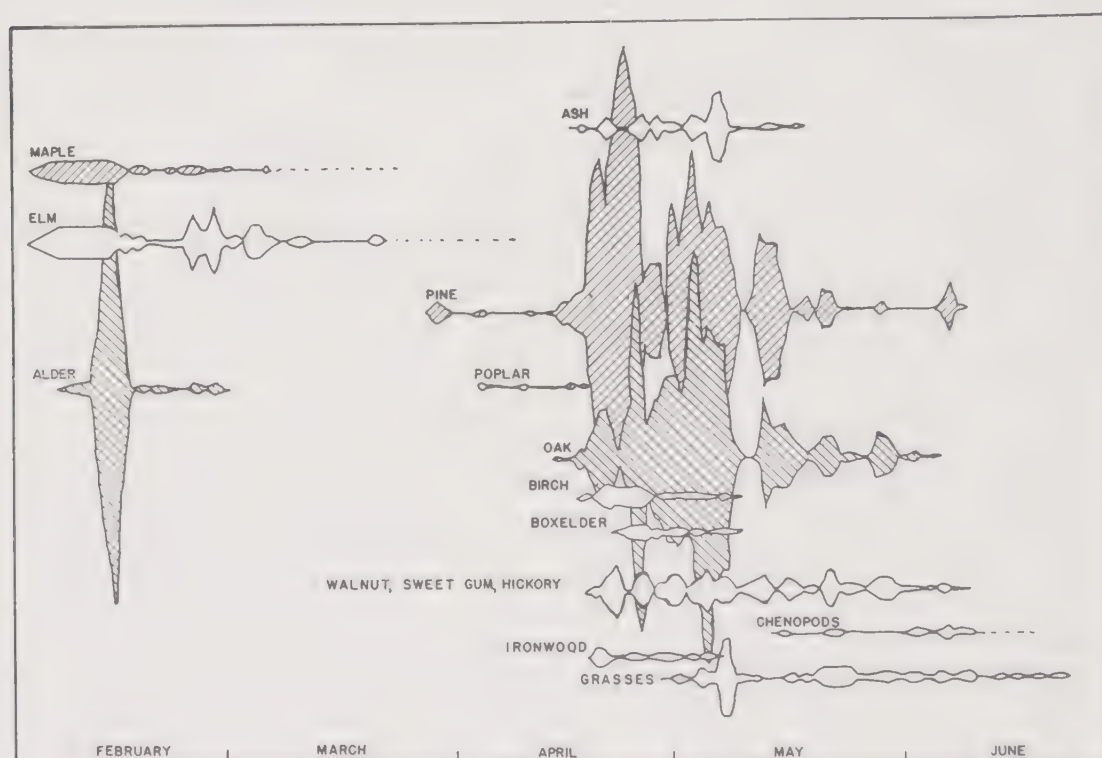


Fig. 103.—Spring pollen incidence, Richmond, 1932.

The unit slide area to be used for purposes of statement, as adopted by the National Pollen Survey Committee of the American Academy of Allergy, is 1 square centimeter. However, the committee has approved of volumetric interpolation for ragweed, using the 3.6 factor. In releasing ragweed figures to the public through newspapers, radio, and similar channels, the cubic yard unit is recommended. One may go farther and make complete volumetric interpolation of figures for all pollen species, but in scientific reports the 1 square centimeter basic unit should always be clearly stated.

CHAPTER XLIII

POLLEN SURVEYS IN THE UNITED STATES AND ADJACENT AREAS

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The need and value of pollen surveys carried out by experienced botanists with some appreciation of the allergy problems involved have been apparent ever since Scheppegrell began stressing the importance of the field aspects of inhalant allergy. From 1916 until the early 20's most of the effort along this line was devoted to field observations of wind-pollinated plants. However, during this time Scheppegrell was experimenting with pollen counting as a check on field studies. His ragweed figures for six seasons in New Orleans as published in 1923 served to initiate similar work in other parts of the country. The first coordinated atmospheric studies to be attempted were those carried out by the author (O.C.D.) with the cooperation of twenty-two physicians, in as many different cities, during the ragweed season of 1928. This was followed by my nationwide study in which the local weather observers of the United States Weather Bureau cooperated in securing air samples. This survey was continued from 1929 until 1944 and included, first and last, about 100 cities and communities. Meanwhile the advantages of combining field and atmospheric studies had been widely recognized so that in many places interested allergists have carried on their own comprehensive survey work continuously over a period of more than two decades.

In this chapter an effort has been made to list the sources of all existing data on field and atmospheric studies of hay fever plants and pollens in the United States, its possessions and the adjoining countries. I have also included clinical evaluations of the more common pollens. Reference to the published articles of most of the workers referred to in the tabulation and discussions will be found in the bibliography at the end of the book. In cases where no reference is given, it may be assumed that these data have not been published but that they are available either from the person named or from the files of the author (O.C.D.). The dates of particular studies are in many instances the actual year in which the work was done, in others the year of publication—usually the year after the survey.

The calendars of pollination for each state are necessarily approximate. The termination of the grass season, for example, is often indefinite. In several places grass pollen has been encountered in appreciable amounts through the late summer and fall and it is not known whether such a finding was typical or not.

Particular attention is called to the ragweed index where a special effort has been made to weigh every scrap of existing ragweed data for more than 300 localities. It should be remembered that in some places where ragweed incidence is low, sagebrush pollen is plentiful. Such places cannot be given unqualified endorsement as fall hay fever refuges, although they usually prove satisfactory. In some places the index is based on a single season's testing. Old Forge, New York, is an example of this. Judged by experience in other points in the area, this figure is lower than it would be if tests had been continued for several seasons.

Alabama

Field Studies:

Montgomery, 1931, Clarence K. Weil, M.D.

Observations at Hamilton, Birmingham, Montgomery, Dothan and roadsides between these points, by author (O.C.D.)

Atmospheric Records:

Birmingham, Marion T. Davidson, M.D.

Mobile, summer and fall, 1931-1933, by author (O.C.D.)

Tree season, January to May.

Grass season, April to September.

Ragweed season, September and October.

Dr. Weil's study, centered at Montgomery, includes a discussion of the statewide problem. His calendar of pollination and his clinical evaluations of the different pollens of the state are the only such locally prepared data available. He regards the ragweeds as of prime importance and says that ragweed pollen "is responsible for over one-half of the hay fever seen in this section and for almost all of the fall cases." He gives the onset of active ragweed pollination as September with only small amounts of pollen before this date. My record for Mobile covering the ragweed seasons of 1931, 1932, and 1933 shows small amounts of ragweed pollen in the air as early as August 10 with no appreciable increase in amount until the first week of September. No average climax date could be established but the season seems to be definitely ended by the twentieth of October. Dr. Davidson's ragweed figures for Birmingham have not been published, but he has furnished sufficient data on which to base a tentative index figure. My observations show that most of the ragweed pollen comes from short ragweed rather than giant ragweed. From Birmingham southward the latter is a rare plant except in the larger cities. No doubt there is a considerable amount of giant ragweed growing in the Tennessee River Valley in the north end of the state. I found a small but insignificant amount of rough marsh elder (*Iva ciliata*) a few miles southeast of Montgomery. More than likely rough marsh elder is common along the Gulf. No other species of ragweed than the above named are abundant enough to be of any clinical importance in Alabama.

Dr. Weil lists annual bluegrass, rye grass, Bermuda grass, and Johnson grass, but does not specify which of these he regards as most important—doubtless Bermuda. The grass season as a whole lasts from March until September in Montgomery, and until late October or possibly longer in Mobile. No atmospheric records are available before August. During the August to October period at Mobile, grass pollen incidence is about one-tenth that of ragweed.

Alabama has a long list of native wind-pollinated trees, but Dr. Weil discusses only six of them. "Elm pollinates from the middle of February until the end of March. The pollen of this species is particularly toxic and causes intense symptoms in a sensitive individual." Quite likely elm pollination begins as early as mid-January when the season is favorable. Records for Atlanta, Georgia (1944), which has approximately the same latitude as Birmingham, showed heavy elm incidence (500 to 600 granules per cubic yard of air) between January 10 and 20. "Hackberry is used as a shade tree even more than elm. Patients are rarely very sensitive in their reactions to this pollen. The pollen of oak is produced in tremendous quantities, and the ground is often covered with the catkins of male flowers. Pollination lasts through the month of March and occasionally into the first part of April." These are probably average dates for Montgomery, Alabama, but in northern Alabama the season certainly lasts throughout April and even into May. Dr. Weil finds that patients reacting to pecan pollen also react to that of other hickories and the walnuts. "Also im-

munization against one will protect against all three. I have seen four cases of pecan hay fever and am convinced that there are hundreds of such cases in the state of Alabama." Cottonwood pollen is also mentioned as a cause of hay fever with a season of pollination "from March 15 to April 15."

Alaska

Atmospheric Records:

Fairbanks, Juneau, and Nome; July, August, and September, 1939, by author (O.C.D.)

No field studies have been reported from any part of Alaska. Complete pollen counts in the three Alaskan cities for one season showed an entire absence of ragweed pollen. If the record for these three cities is typical the possibility of inhalant allergy from pollens and spores in Alaska is remote or confined at most to a few days of light exposure during the grass season in late June and early July in southern and central Alaska.

Arizona

Field Studies:

Statewide survey, 1922, S. H. Watson, M.D. and C. S. Kibler, M.D.

Central Arizona, 1934, E. A. Gatterdam, M.D.

Phoenix, 1926-1939, E. W. Phillips, M.D.

Phoenix, 1947, C. W. Vivian, M.D.

Williams, Flagstaff, Seligman, Kingman, Winslow, Holbrook, 1931-1934, R. W. Lamson, M.D. and Alva Watry.

Yuma, 1936, George F. Harsh, M.D.

Observations in Kiabab National Forest, Yuma, Phoenix, Tucson, Douglas and points between, also Flagstaff, Winslow, Holbrook, Alantown and points between, by author (O.C.D.)

Combined Field and Atmospheric Studies:

Phoenix, 1944, Howell S. Randolph, M.D., and Margaret McNeil.

Grand Canyon National Park, summer and fall, 1946, 1947, by author (O.C.D.)*

Atmospheric Records:

Phoenix, 1929, 1933, by author (O.C.D.)

For the state as a whole Drs. Watson and Kibler believe that the chenopods and amaranths should be regarded as the most important offenders, Palmer's amaranth being particularly abundant in the cultivated areas and the saltbushes in the desert. Commenting on the situation in the Salt River Valley, of which Phoenix is the central point, Dr. Phillips says: "In this valley the cottonwood, ash, and olive trees cause mild symptoms in February, March, and April, respectively. Bermuda grass blooms from April 1 to late November, causing intense symptoms. There is no true ragweed in the valley, but members of an allied genus, *Franseria*, cause two ragweed seasons: the first, in March and April, from the desert franserias; the second, in September and October, from the false ragweed. Various species of *Chenopodiales*, including careless weed and Russian thistle, cause weed hay fever in summer; careless weed blooms in protected places most of the year. Visitors who are sensitized to the eastern ragweeds are not affected by the franserias unless they are group sensitized. Newcomers who had grass hay fever in the East do not react to the pollen of Bermuda grass until after several years of exposure. Visitors sensitive to pigweed or Russian thistle are not annoyed by pollen of the local species in winter, but they are liable to have symptoms in their first summer. All such group reactors are promptly relieved by intradermal treatment with extracts of the appropriate local pollens."

*With the cooperation of National Park Service and Utah Parks Company.

Dr. Randolph's comments and statistical table follow: "Although appearing in small numbers throughout the entire season, careless weed (*Amaranthus palmeri*) is essentially a late summer and fall weed, and is the most important pollen producer from August to November. Russian thistle (*Salsola pestifer*) and slender false ragweed are of less importance. From observation of the Russian thistle plant it seems to have been spreading during the past ten years. The slender false ragweed is not numerous, but has to be considered a cause of symptoms in October. The common ragweed, so important in the Midwest, is not found here."

TABLE XXXIV. COMPARATIVE TABLE OF POLLEN GRAINS

POLLEN	DESERT		CITY	
	NUMBER	PER CENT	NUMBER	PER CENT
Bermuda	807	8.86	3996	24.28
Johnson	772	8.47	961	5.84
Cottonwood	1055	11.58	2588	15.72
Ash	820	9.00	2674	16.25
Careless Weed (Palmer's amaranth)	3447	37.83	1575	9.57
Sl. False Ragweed	336	3.69	320	1.94
Rabbit Bush (False Ragweed)	445	4.88	464	2.82
Olive	206	2.26	405	2.46
Pine	113	1.24	121	0.73
Walnut	25	0.27	24	0.14
Miscellaneous	244	2.67	2038	12.38
Unidentified	841	9.23	1293	7.85
Total Number	9111	99.98	16459	99.98

"Table XXXIV represents a comparison between the pollen incidence in the city and that one mile from the edge of irrigation. Particularly interesting is the low incidence of spring pollinating pollen on the desert as compared to the city, and the relatively lower total pollen count. A notable exception, however, is the rabbit bush and the fall pollinating careless weed. Probable explanation of the high careless weed count on the desert is the fact that a large part of this pollen is produced in the citrus groves during the fall season when weeds are allowed to grow as a cover crop. These groves are located along the edge of the Valley in a belt about two miles wide, adjacent to the desert."

Another locally important source of chenopod pollen in the Salt River Valley is sugar beet. The culture of sugar beets for seed in this area began about 1937. Pollen production is enormous in April and May. Allergies who are sensitive to Palmer's amaranth and Russian thistle are also sensitive to sugar beet pollen. In the cultivated areas of northern Arizona, Russian thistle is present and occasionally abundant.

Ragweeds, including false ragweeds, of no less than a dozen species are scattered sparingly throughout the state. Three shrubby false ragweeds, *Franseria dumosa*, *F. ambrosioides* and *F. deltoidea*, found in the Salt River Valley and southern part of the state shed pollen only in the spring. All others are fall pollinators. The principal source of fall ragweed pollen in the southern part of the state is slender false ragweed (*Franseria tenuifolia*). In the north part there is some western ragweed and a fair sprinkling of false ragweed (*Franseria acanthicarpa*). Lamson and Watry do not mention this species in their study of cities along the Santa Fe Railroad but I found it a common roadside weed between Winslow and Holbrook. Sagebrush is more abundant in the northern part of the state than ragweed. Some desert areas, for example, the Prismatic Plains, support vast acreages of almost pure sagebrush. Junipers (*Juniperus utahensis* and *Juniperus monosperma*) are common at higher altitudes in the northern part of the state.

Harsh lists the following as locally important pollens at Yuma: Bermuda grass, quailbrush (*Atriplex lentiformis*), pecan and Palmer's amaranth.

Slides exposed at the South Rim at Grand Canyon showed traces of pollen of sagebrush, ragweed, chenopod and grass. Their relative importance can be judged by the following figures showing the highest catch of each of these pollens on any one day during the season of 1947: sagebrush, 4 pollens per cubic yard of air, ragweed 4, chenopod 1, grass 2. Thus, even with the presence of some sagebrush, the South Rim of Grand Canyon may be regarded as a safe refuge from ragweed and related pollens. Field observations on the North Rim and in surrounding areas indicate an equally favorable rating.

Arkansas

Field Studies:

Little Rock, Hot Springs, area along Mississippi opposite Memphis and incidental observations along the western edge of the state at various times, by author (O.C.D.)

Atmospheric Records:

Little Rock, summer and fall, 1947, A. G. Cazort, M.D.

Little Rock, summer and fall, 1931-1933, by author (O.C.D.)

West Memphis, see Memphis, Tennessee.

Tree season, February to April.

Grass season, May and June.

Ragweed season, mid-August to mid-October, apex varies from September 6 to September 18.

Short ragweed and giant ragweed are without question the outstanding sources of hay fever pollen throughout the state of Arkansas. Other ragweeds found in the state include southern ragweed (*Ambrosia bidentata*), rough marsh elder (*Iva ciliata*) and narrow-leaved marsh elder (*Iva angustifolia*). Southern ragweed is abundant in some cultivated areas at least in the north and eastern parts of the state and rough marsh elder in the lowlands along the Mississippi. The narrow-leaved species is reported as common in Sebastian County. The pollen of these three ragweed species cannot be readily distinguished from that of giant or short ragweed in atmospheric tests. No other fall pollen is abundant enough or active enough to cause allergic difficulty, except perhaps the fall pollinating scrub elm (*Ulmus crassifolia*) found in the southern part of the state.

Arkansas grasses include both northern and southern types—bluegrass, timothy, orchard grass, Bermuda grass and Johnson grass. Bermuda and Johnson grass are known to shed pollen all through the summer and early fall, but certainly the amount of any sort of grass pollen in the air as proved by atmospheric tests is extremely small during the ragweed season.

Many varieties of spring pollinating trees doubtless shed as great amounts of pollen as are encountered in surrounding states. The nearest point where field checks of trees have been made is Memphis. See summarized tree data in the discussion for Tennessee.

California

Field Studies:

Statewide survey, 1922, H. M. Hall.

Northwestern California, 1935, A. H. Rowe, M.D., and J. W. Howe.

Southern California, 1926, George Piness, M.D., Hyman Miller, M.D., and H. E. McMin.

Southern California, 1946, Willard S. Small, M.D., and Grace M. Small.

San Joaquin County, 1932, A. H. Rowe, M.D.

Needles, 1944, Alva Watry and R. W. Lamson, M.D.

San Francisco, 1929, A. H. Rowe, M.D.

Barstow and Santa Ana, 1944, R. W. Lamson, M.D., H. McMichael and M. Stiekler.
 Observations in Alameda County, Bakersfield, Dorris, Dublin, Fresno, Lindsay, Los Angeles, Merced, Modesto, Mojave Desert, Napa Valley, Redlands, Riverside, Sacramento Valley (Upper), San Bernardino, San Diego, San Francisco, San Joaquin County, Shasta and Tule Lake—23 of 58 counties, by author (O.C.D.).

Combined Field and Atmospheric Studies:

Imperial County, 1936, George F. Harsh, M.D.
 San Diego County, 1945, George F. Harsh, M.D.
 East shore of San Francisco Bay, 1927, A. H. Rowe, M.D.
 Lassen Volcanic National Park, 1947, by author (O.C.D.).*
 Yosemite National Park, 1946, 1947, by author (O.C.D.).†
 Sequoia-King's Canyon National Parks, 1946, 1947, by author (O.C.D.).*

Atmospheric Records:

Arcata, 1938, W. C. Deamer, M.D., H. L. Jenkins and D. S. Lazarus.
 San Francisco, 1935, W. C. Deamer, M.D., and H. E. McMinn.
 Los Angeles, summer and fall, 1929, 1933, 1936, by author (O.C.D.).
 Los Angeles, summer and fall, 1946, A. M. Targow, M.D.
 Sacramento, summer and fall, 1933, by author (O.C.D.).
 San Diego, 1936, C. L. Stealy and H. McMichael.
 Pasadena, 1947, Willard S. Small, M.D.

In no state are weather, climate, topography and soil conditions so varied and their effect on pollen production and distribution so marked as in California. Consequently very few general statements can be made about hay fever flora or pollen incidence in this state. It is strongly urged that the reader consult the original publications mentioned above, particularly the later ones.

More than 30 species of ragweed (*Ambrosiaceae*), mostly false ragweeds (*Franseria* spp.), are listed by Rydberg as growing within the borders of the state, but at no time or place has a reported atmospheric record of ragweed pollen for one day exceeded 20 granules of pollen per cubic yard of air (see indices, page 524). Annual totals have not exceeded 1 or 2 per cent of the average annual totals for ragweed pollen in the central Mississippi Basin, except at Arcata, a town of 2,000 people, in the northwest corner of the state, and at Alpine, a village of 200, some 50 miles from the coast in San Diego County. This does not mean that every other part of California offers perfect refuge from ragweed and from antigenically related air-borne pollens. Local exposure is possible in cultivated fields and orchards, particularly in irrigated areas. It is also possible for ragweed sufferers to be affected by the pollen of any species of sagebrush (*Artemisia*). On the hills and low mountains near the coast in southern California, sagebrush pollen is sometimes encountered in quantities equal to or exceeding that of ragweed. The rabbit bushes (*Chrysothamnus* spp.), although basically insect-pollinated shrubs, are very abundant in many parts of the state and in some very dry windy areas are the source of small but appreciable amounts of air-borne pollen that contains an allergenic substance of similar quality and potency to that of ragweed.

Ragweed sufferers moving from the middle and eastern states to the populous areas of California are advised by California allergists that they will likely be free of ragweed hay fever symptoms for several years, but sooner or later develop sensitivity to other more abundant local pollens. Inland along the southern border of the state ragweed pollen may appear in the air as early as March from any or all of the three shrubby false ragweeds, *Franseria dumosa*, *F. deltoidea* and *F. ambrosioides*. At San Diego the beach bur (*Franseria bipinnatifida*) also sheds pollen in the spring as well as throughout the summer and fall.

*With the cooperation of National Park Service.

†With the cooperation of National Park Service and Yosemite Park & Curry Company.

Of the autumn blooming ragweeds, western ragweed (*Ambrosia psilostachya*) is certainly the most abundant and widely distributed species throughout the state. It is probably the chief source of ragweed pollen in the northern third of the state. Harsh regards it as the principal source in San Diego County.

False ragweed (*Franseria acanthicarpa*) is listed by Piness as the most important ragweed in Los Angeles. It is fairly common in fields and on roadsides from Madeira County southward to the Tehachapi Mountains. Small regards western ragweed and false ragweed as of equal importance in the irrigated orchards throughout southern California.

Harsh says of *Franseria dumosa*, "The chief cause of ragweed pollinosis in Imperial County." However, Small stresses burrow bush (*Hymenoclea salsola*), a spring blooming ragweed, for this same area.

The National Park areas in the High Sierras and the Cascades—Lassen, Yosemite, and Sequoia-King's Canyon—offer almost perfect protection from ragweed and related pollen as has been proved by my own inspection of the flora of the parks and the surrounding areas, as well as the results of air sampling and counting through one season in each of the three parks (see indices, page 524). Ragweeds are entirely absent and sagebrush (*Artemisia*) of any sort is absent or relatively nonproductive in the National Parks of California, except perhaps in Yosemite. The stray grains of ragweed pollen caught on test slides in these parks certainly originates some distance from their boundaries.

The most important members of the sagebrush family (*Artemisia*) are mountain sagebrush (*Artemisia tridentata*), California mugwort (*A. heterophylla*) and coastal sage (*A. californica*). Mountain sagebrush is typical of the basin area of the extreme northeast corner of the state and of the interior deserts and bordering mountains of the south (Imperial County and central part of Riverside County). California mugwort is found throughout the state in lowlands and hills. Piness considers mugwort to be much more important than any other species in southern California except in Imperial County. He says, "Mugwort is perhaps the most frequent cause of the fall type of hay fever. It is very common in low ground and hills of the entire central and western parts of the region (southern California). It pollinates profusely from July to the middle of September, often continuing until late October in some places." Coastal sage is typical and frequently the dominant plant species on the low coastal mountain ranges from San Francisco southward. All of these sages pollinate in late summer and fall. In 1933 Deamer and McMinn found coastal sage pollen to be more than five times as abundant in the air in San Francisco as the pollen of the ragweeds.

Regarding the pollination of coastal sage, Small says: "On the hills surrounding the interior valleys and on the foothills of the inland ranges its habits of pollination are variable. . . . It begins to form buds in late September. After the first good autumn rain these grow, and almost exactly 18 days after the rain these buds burst into bloom, the pollen being all dissipated in about a week. Some years when there are light rains in the fall some bushes, apparently those receiving enough moisture, will bloom while others will await heavier rains. In 1939 the majority of these plants pollinated two weeks in the middle of January after a dry fall and heavy rains the first of January."

In San Diego County the pollen of coastal sagebrush has been found to reach atmospheric concentrations of 78 pollen grains per cubic yard of air. This is higher than any other recorded California figure for sage pollen—considerably higher than figures for ragweed. It ranks with results of air tests for sagebrush pollen in Wyoming and Idaho.

If the variety of California ragweeds is impressive the variety of chenopod-amaranths (*Chenopodiales*) is overwhelming. There are nearly three times as many. Nevertheless, in the three most populous communities of the state, San Francisco, Los Angeles and San Diego, the group as a whole has been proved by atmospheric tests and clinical experience to be less important than the ragweeds and sages and far less important than the grasses. This is also true at Arcata but not in Imperial County where the chenopod-amaranths are more important than any other weed group. The outstanding offenders in the chenopod-amaranth group are the saltbushes (*Atriplex spp.*), Russian thistle (*Salsola pestifer*) and Palmer's amaranth (*Amaranthus palmeri*), also known as careless weed. The latter, which seems to be the only really important amaranth in California, is confined for the most part to the irrigated areas of Imperial County, where it sheds pollen from April to November. Outside of the Imperial Valley I have seen only one heavy local infestation—a small, badly contaminated cotton field near Bakersfield.

The saltbushes include numerous species of annual, perennial, and shrubby plants. The annual species, which include annual saltbush (*Atriplex wrightii*), sparscale (*A. patula* or *hastata*), bractscale (*A. bracteosa*), redscale (*A. rosea*), and silverscale (*A. argentea*), reach their highest development in salt marshes along the coast and in the cultivated alkaline soils of the interior valleys where Russian thistle also flourishes. The pollinating season for these saltbushes and Russian thistle is, roughly, June to September. The shrubby saltbushes, of which shadscale (*Atriplex canescens*), lenscale (*A. lentiformis*) and allscale (*A. polycarpa*) are probably the most important, are plants of the desert and mountain slopes.

Chenopod pollen is extremely rare in the air at Lassen Volcanic National Park and at Yosemite National Park. In Sequoia National Park the amount is somewhat more than in the other two parks but still far less than in the San Francisco Bay area where Rowe regards it as of questionable importance.

Aside from the composites (including the ragweeds and sages) and the chenopod-amaranths, the only California wind-pollinated weeds that need be mentioned are English plantain and the docks (*Rumex spp.*). English plantain is known to be a hay fever factor only in the San Francisco Bay region and from there northward along the coast. The aerial incidence of plantain pollen in these areas is considerably greater than in any point east of the Cascades and Sierras where air tests have been made. Northern California figures compare favorably with those of western Washington and western Oregon. In Rowe's survey of the San Francisco Bay region the pollens of plantain and dock (not distinguished in counting) equalled in amount that of all other weeds. Pollination occurred mostly in April, May, and June. At Arcata on the north coast Deamer found more English plantain pollen than any other kind except grass. Pollination was heaviest through June, July, and August with small amounts from May to November.

The evaluation of grass pollens has been a more difficult task in California than in the central and eastern states where the bulk of the air-borne grass pollen comes from a small list of hay and meadow grasses: bluegrass, timothy, orchard grass, redtop. While these grasses are also planted in the cooler parts of California their acreage is restricted and the season of bloom variable. They are only locally important in California. Even the wild grasses and "weed-pest" grasses vary greatly in distribution and season. All local authorities agree that Bermuda grass is the outstanding grass offender in the populous



FIG. 104.—This map shows the more than 300 places where atmospheric tests have been made over periods from 1 to 20 seasons as covered by the discussion for each state, province, and country.

TABLE XXXV. CALIFORNIA

	Western Ragweed (<i>Ambrosia psilostachya</i>)	False Ragweed (<i>Franseria cumbicarpa</i>)	Beach Bur (<i>Franseria bipinnatifida</i>)	Desert Ragweed (<i>Franseria dumosa</i>)	Cocklebur (<i>Xanthium</i> spp.)	Mountain Sagebrush (<i>Artemisia tridentata</i>)	Coastal Sage (<i>Artemisia californica</i>)	California Mugwort (<i>Artemisia heterophylla</i>)	Palmer's Amaranth (<i>Amaranthus palmeri</i>)	Pigweed (<i>Amaranthus retroflexus</i>)	Lamb's Quarters (<i>Chenopodium album</i>)	Russian Thistle (<i>Salsola pestifer</i>)	Burning Bush (<i>Kochia scoparia</i>)	Shadscale (<i>Atriplex canescens</i>)	Australian Saltbush (<i>Atriplex semibaccata</i>)	Alscale (<i>Atriplex polycarpa</i>)	Quailbrush (<i>Atriplex lentiformis</i>)	Bractscale (<i>Atriplex bracteosa</i>)	Spearscale (<i>Atriplex hastata</i>)	Silverscale (<i>Atriplex argentea</i>)	English Plantain (<i>Plantago lanceolata</i>)
Dorris						X						X	X	X					X		
Arcata	X		X		X			X			X								X		X
Redding								X													X
Sacramento	X				X			X		X	X	X									X
Stockton	X				X			X		X	X	X									X
Oakland area	X		X		X			X			X								X		X
San Francisco			X		X		X	X		X									X		X
Merced	X							X				X						X			
Fresno	X	X						X		X			X								
Lindsay	X	X						X				X									
Bakersfield	X	X						X		X	X	X		X		X	X				X
Barstow				X								X		X							
Los Angeles	X	X			X		X	X		X	X	X						X	X	X	
Pasadena	X	X			X		X	X		X	X	X						X	X	X	
Riverside	X	X						X		X		X									
San Bernardino	X	X						X		X	X	X									
Santa Ana	X	X			X		X	X		X	X						X	X	X	X	
Oceanside	X		X				X								X						
Esecondido	X						X			X					X						
San Diego	X		X				X				X	X									
Alpine	X						X														
El Centro									X			X					X				
Brawley				X					X		X						X				

HAY FEVER FLORA

Bermuda Grass (<i>Cyniola dactylon</i>)	Annual Bluegrass (<i>Poa annua</i>)	Bluegrass (<i>Poa pratensis</i>)	Orchard Grass (<i>Dactylis glomerata</i>)	Timothy (<i>Phleum pratense</i>)	Redtop (<i>Agrostis palustris</i>)	California Brome Grass (<i>Bromus carinatus</i>)	Soft Brome Grass (<i>Bromus mollis</i>)	Bromus Grass (<i>Bromus rigidus</i>)	Canary Grass (<i>Phalaris minor</i>)	Foxtail Fescue (<i>Festuca megalura</i>)	Johnson Grass (<i>Sorghum halepensis</i>)	Salt Grass (<i>Distichlis spicata</i>)	Rye (<i>Secale cereale</i>)	Rye Grass (<i>Lolium multiflorum</i>)	Wild Oats (<i>Avena fatua</i>)	Wall Barley (<i>Hordeum murinum</i>)	Velvet Grass (<i>Anthus lanatus</i>)	California Black Walnut (<i>Juglans californica</i>)	English Walnut (<i>Juglans regia</i>)	Coast Live Oak (<i>Quercus agrifolia</i>)	Oak (deciduous) (<i>Quercus laevis</i>)	Cottonwood (<i>Populus fremontii</i>)	Sycamore (<i>Platanus racemosa</i>)	Olive (<i>Olea europaea</i>)	Alder (<i>Alnus rhombifolia</i>)
X			X			X			X			X		X			X					X			X
	X										X			X						X			X		
X						X	X			X	X	X		X	X	X							X		
X						X	X			X	X	X		X	X	X							X		
X	X	X	X	X	X	X	X		X	X		X			X		X	X						X	
X	X				X									X	X										
X		X	X	X	X						X				X								X		
X															X								X		
X															X							X	X	X	X
X							X					X						X				X	X	X	X
X																									
X																									
X						X					X														
X						X		X	X		X	X		X	X			X	X	X		X	X	X	X
X						X	X							X	X					X	X	X			X
							X	X		X					X	X				X	X				

districts of southern California. It is also found in all lower elevations in the central valleys and the whole coastal area. However, it is not considered the dominant grass in the Bay region or along the north coast. Here the rye grasses are more important.

In southern California Bermuda grass will pollinate during any month of the year when there is enough rainfall to encourage growth or where irrigation is continuous. Incidence is heaviest in Imperial Valley in the months of April, May, and June. In San Diego there is some grass pollen in the air practically every day in the year with minimum quantities in December, January, and February. In San Francisco and the Bay region heaviest incidence occurs usually in April, May, and June. Sometimes the season lasts through August. Here, also, some grass pollen can be found in the air every month of the year. At Arcata grass pollen incidence is heavy from late April to late October. In 1936 the highest incidence occurred in June. Some pollen was found during every month except January.

The amount of grass pollen found in the air in southern California and the San Francisco area during the whole season compares very favorably with the amount found during the six-week grass period in the central states. The totals for Arcata on the north coast are much higher than any central states figures so far published, comparing favorably with the heavy incidence found in western Washington.

In Hall's list of 175 wind-pollinated plants of California only about 20 trees are included. Of these the only one rated as of general importance in allergy is California black walnut (*Juglans californica*). The forested regions of the state support heavy growths of the conifers whose pollen is almost entirely nontoxic. The one important exception is incense cedar found at elevations between 3000 feet and 5500 feet in the Sierra Range. The pollen of this tree is shed in midwinter. The pollen of Monterey cypress (*Cupressus macrocarpa*) is said to be mildly active. In the coast ranges several species of oak shed moderate amounts of pollen during the late spring. In irrigated desert areas cottonwood pollen is sometimes very annoying. The California black walnut mentioned above, according to Hall, is "much grown as a shade and ornamental tree in the Sacramento, Napa and Russian River Valleys; here the most frequent cause of spring hay fever; less common in the San Joaquin Valley and the south coast ranges; occurs native especially at Walnut Creek and in the coastal canyons of southern California from the Santa Ana Mountains north; common in the hills back of Los Angeles and Santa Monica, often near suburban homes." Season of pollination, April and May. Other trees of local importance are noted in Table XXXV.

Colorado

Field Studies:

- Statewide, 1930, Robt. F. E. Stier, M.D., Guy Hollister, and Thomas A. Bonser.
- Central Colorado, 1926, J. J. Waring, M.D.
- Mesa Verde National Park, 1947, by author (O.C.D.)
- Pikes Peak region (Colorado Springs), 1934, W. C. Service, M.D.
- Denver, 1928, L. A. Conway, M.D.
- Denver, 1932, T. D. Cunningham, M.D., and A. M. Wolfe.
- Denver, 1938, R. P. Johnson, M.D.
- Colorado Springs, 1923, Wm. V. Mullin, M.D.
- Greeley and vicinity, 1934, A. M. Poole, Ph.D.
- Pueblo, 1924, J. G. Wolf, M.D.

*With the cooperation of National Park Service.

Observations in eastern, central and southern Colorado, including the following cities and towns in 27 counties: Alamosa, Colorado Springs, Cortez, Durango, Fort Collins, Fort Morgan, Greeley, Julesburg, Laird, Lamar, Limon, Longmont, Loveland, Pueblo, Sterling, and Walsenburg, 1925-1947, by author (O.C.D.)

Combined Field and Atmospheric Studies:

Rocky Mountain National Park, 1944, 1947, by author (O.C.D.)*

Denver (city and county), 1925, J. J. Waring, M.D.

Denver, summer and fall, 1929-1934, 1937, by author (O.C.D.)

Atmospheric Records:

Eastern Colorado, see Goodland, Kansas.

Colorado Springs, August-September, 1947, W. C. Service, M.D.

Pikes Peak, summer and fall, 1934, by author (O.C.D.)

Tree season, March and April.

Grass season, June to mid-July.

Chenopod season, July to mid-September.

Ragweed season, August and September.

Sage season, August and September.

Twenty-five years ago excellent field studies of hay fever plants were being carried out in Colorado, Dr. Mullin's report for Colorado Springs being one of the very first local studies to appear in the periodical medical literature. It was followed shortly by reports on Denver and central Colorado by Dr. Waring. Many later field surveys have been made, mostly within the central populous area of the state, but, unfortunately, there are little or no data for the north-western quarter of Colorado. No atmospheric studies have been carried on outside of Denver, Colorado Springs, and Rocky Mountain National Park.

The accuracy and thoroughness of the field studies by Miss Maxey Pope in the Waring surveys have seldom been equalled anywhere. No atmospheric tests were made outside of Denver but other effective methods were used in evaluating the local importance of wind-pollinated plants and in checking their seasonal performance in 40 cities and towns.

The ragweeds are very important in Colorado. In the dry farming and grazing area of the eastern third of the state the common ragweeds of the Mississippi Valley are not plentiful, being replaced by burweed marsh elder (*Iva xanthifolia*) and by scattered patches of western ragweed (*Ambrosia psilostachya*) and occasional pure stands of false ragweed (*Franseria acanthicarpa*). For the state as a whole burweed marsh elder is the most conspicuous member of the family. It is present in most towns and in practically all neglected irrigated land. In the eastern part of the state it furnishes almost 100 per cent of airborne ragweed pollen. (See comments on this plant in Kansas discussion.) In Denver the proportion is only one-third (records for 1933 and 1934). The other two-thirds probably come mostly from short ragweed and giant ragweed with smaller quantities from western ragweed and false ragweed. In the mountainous parts of the state up to 7,000 feet altitude, ragweeds, particularly burweed marsh elder, are likely to be found in diminishing amounts in all cultivated land and often by roadsides, but are absent from meadows and wooded areas. Above 7,000 feet ragweeds of any kind are scarce or much stunted, or both. The season of highest aerial incidence of ragweed pollen occurs in August and early September. Western ragweed may reach anthesis as early as July but the output of its pollen is small. Termination of the Colorado ragweed season for the central and western parts of the state is at least ten days earlier than in the central and northern Mississippi Valley.

Colorado doubtless has many ragweed-free, or practically free, areas, but certainly Colorado Springs is *not* one of them, popular tradition to the contrary notwithstanding (see index, page 524). Estes Park and Grand Lake are the only places that have so far been certified in this respect. Even in these and other points in the mountains where ragweed is absent the ragweed sensitive person is exposed to appreciable amounts of sagebrush pollen. This pollen is not irritating to some ragweed sufferers. The reports from ragweed sensitive visitors to the Rocky Mountain National Park are nearly always favorable.

True sagebrush (*Artemisia tridentata*) is confined to the Rocky Mountain section of the state. Pasture sage (*A. frigida*) is scattered throughout the foothills and mountain valleys and sand sagebrush (*A. filifolia*), or silvery wormwood, grows locally in virgin soil on the eastern prairie areas, being particularly luxuriant in the southeast corner of the state. The season of pollination of all members of the sagebrush family is mostly in August and September.

Throughout the state, in cities, towns, fields, and wastelands, the chenopods (*Chenopodiaceae*) are usually more abundant, more conspicuous and often more productive than all of the ragweeds. Two plants are outstanding—Russian thistle (*Salsola pestifer*) and burning bush (*Kochia scoparia*), often referred to as Kochia. The latter seems to be increasing and tending to supplant the former. Russian thistle pollen is highly toxic, probably more so than ragweed pollen, certainly more so than that of Kochia. The season of pollination of the chenopods occurs mostly in July and August with a small amount of pollen still flying in early September. In the wheat belt along the Kansas border almost all of the local hay fever sufferers are clinically sensitive to the chenopods and not to the ragweeds even though they encounter large amounts of burweed marsh elder pollen. Proof of specific chenopod sensitiveness in these cases is found in the lack of skin reactions to any kind of ragweed pollen and in freedom from symptoms outside the Russian thistle area even when exposed to excessive amounts of ragweed pollen, as in Missouri and Illinois. The saltbushes (*Atriplex* spp.) are found in central and southern Colorado but their productivity is lower than the annual chenopods just discussed.

Palmer's amaranth (*Amaranthus palmeri*), a very important cause of hay fever in the Southwest, is present in a few places in Colorado but probably nowhere abundant enough to be considered as a clinical factor.

The following comparisons are drawn from Service's 1947 pollen survey: maximum figure for any one day (pollen grains per cubic yard of air), ragweed 122, sagebrush 48, Russian thistle 21. Accumulated seasonal total, ragweed 1,324, sagebrush 778, Russian thistle 275.

Grass pollens are not nearly as important in Colorado as in the Mississippi Valley and the eastern states. Wild grasses used for hay and grazing, such as the wheat grasses (*Agropyron* spp.) and grama grasses (*Bouteloua* spp.), are not heavy producers. In cities and in mountain valleys, particularly of western Colorado, there is some exposure to the pollen of bluegrass and timothy. Most of the air-borne grass pollen is encountered in June and July.

Tree pollens as a whole are decidedly unimportant. Cottonwoods (*Populus* spp.) are widely distributed in towns, along water courses and in valleys. The pollen causes occasional cases of very severe allergy. American elm (*Ulmus americana*) and Chinese elm of several horticultural species are planted in many of the towns and cities. These, with wild species of juniper (*Juniperus* spp.), should be taken into account in testing for hay fever symptoms occurring in early spring.

Connecticut

Field Studies:

Statewide, 1936, Jay N. Fishbein, M.D.

Atmospheric Records:

Bridgeport, summer and fall, 1938, Harry Resnik, M.D.

New Haven, summer and fall, 1946, 1947, B. P. Freedman, M.D.

Waterbury, summer and fall, 1944-1947, S. W. Jennes, M.D.

Sherman, summer and fall, 1937, by author (O.C.D.)

Observations at Hartford, New Haven, and Bridgeport—6 of 8 counties, by author (O.C.D.)

Tree season, March to May.

Grass season, May to July.

Ragweed season, August and September.

There have been no recent field studies reported for Connecticut. Probably because of the small size of the state and its proximity to the several thorough surveys in the New York metropolitan area and Providence, Rhode Island, it has been thought unnecessary to give special attention to the flora of this state. Ragweeds, short and giant, and the common grasses of the New England and central Atlantic seaboard, constitute the chief hay fever offenders. For evaluation of the tree pollens, also that of plantain, see discussions for Rhode Island and New York. See also ragweed indices for Connecticut cities, page 524.

Delaware

No pollen studies of any kind have been reported for Delaware. Casual observations by the author (O.C.D.) at Wilmington and New Castle suggest that conditions in the populous northern end of the state where the ragweeds are the outstanding offenders may be safely inferred from the findings at Philadelphia, which see.

District of Columbia

Field Studies:

Washington, 1923, 1925, 1928, 1930, H. S. Bernton, M.D.

Washington, 1927, 1944, Grafton T. Brown, M.D.

Observations through the years by the author (O.C.D.)

Atmospheric Records:

Washington, 1937-1941, Grafton T. Brown, M.D.

Washington, 1946, 1947, Eloise W. Kailin, M.D.

Washington, summer and fall, 1929-1944, by author (O.C.D.)

Tree season, February to May.

Grass season, May to July.

Plantain season, June to September.

Ragweed season, August and September.

The ragweeds, short and giant, are the source of 90 per cent of the air-borne weed pollen of the District of Columbia and surrounding areas. According to Dr. Brown ragweed pollen is the cause of "practically all" cases of fall hay fever in the vicinity. Dr. Bernton tabulated 100 cases of inhalant allergy and found that 70 of the sufferers were basically sensitive to ragweed, 13 to the grasses and plantain and 4 to various tree pollens. Brown separated the plantain cases from 100 early summer cases and found that plantain sensitiveness accounted for 6 of them.

Dr. Kailin's 1947 study of air-borne pollen in the District showed an incidence of paper mulberry pollen many times as great (late April and first half of May) as the average recorded by Dr. Brown during the years 1937 to 1941

—the largest, in fact, ever reported in any local study. Brown and Kailin agree that the oaks, sycamores and elms are heavy producers of pollen. They also agree that appreciable amounts of grass pollen and some plantain pollen may be found in the air throughout the late summer and fall.

Brown rates chenopod pollen as “an extremely rare cause of hay fever” in the area. The average annual catch of sage or mugwort (*Artemisia spp.*) pollen, according to this same investigator and confirmed by the author (O.C.D.), is on the order of 0.2 of 1 per cent of ragweed production. So any sage skin reactions on local allergies must be regarded as cross reactions to ragweed rather than evidence of specific sage sensitiveness.

Florida

Field Studies:

State as a whole, but particularly Tampa, Jacksonville, Arcadia, and Sarasota, 1932, 1939, F. C. Metzger, M.D.

State as a whole (spiny amaranth only), 1930, C. J. Heinberg, M.D.

Miami Beach (Australian pine only), 1942, Nelson Zivitz, M.D.

Observations at Jacksonville, Gainesville, Miami Beach, 1928, and on west coast, east coast, Orlando, Kissimmee River, Lake Okeechobee, Everglades (Tamiami Trail), and the Florida Keys—29 of 67 counties, 1940, by author (O.C.D.)

Combined Field and Atmospheric Studies:

Miami and Coral Gables, 1928-1930, E. S. Nichol, M.D. and O. C. Durham.

Atmospheric Records:

Miami, summer and fall, 1929, by author (O.C.D.)

Jacksonville, summer and fall, 1930, by author (O.C.D.)

Tampa, 1931-1933, by author (O.C.D.)

Incomplete records from tests made by F. C. Metzger, M.D., during the fall of 1932 at Orlando, Pensacola, Perry, Sarasota and West Palm Beach, slides counted by the author (O.C.D.)

The heavy rainfall throughout Florida and the lack of heavy frosts over most of the state account for a varied flora and a pattern of distribution of air-borne pollen differing considerably from that of the central, northern and eastern states. Hay fever pollens have been found in the air in southern Florida (Coral Gables) during every month of the year. Tree and shrub pollens are abundant in the air in some places during the winter and early spring but grass and ragweed pollen incidence is always comparatively low as far as present records are concerned.

Ragweeds have been observed in full bloom in considerable acreage in truck gardens at Fort Lauderdale in early June, indicating that they had begun to shed pollen as early as May 25. Similar observations have been made at Tampa and Sarasota. In many places ragweeds remain alive at least until late November. However, the season of greatest ragweed suffering and highest atmospheric incidence of ragweed pollen have occurred during the months of August, September and October. In no case have concentrations been known to exceed 30 granules of ragweed pollen per cubic yard of air for any one day. Throughout the state there is little if any giant ragweed. Short ragweed is present throughout the state in suitable alluvial soil. In Levy County from the Suwanee River to Williston I have observed specimens of short ragweed 9 feet high and heavy growths of cocklebur 6 feet high. These plants and the short ragweeds observed at Gainesville were mostly vegetative, shedding only meager amounts of pollen. Short ragweed is abundant along roadsides where the Kissimmee River empties into Lake Okeechobee. No ragweeds of any kind were found along the Tamiami Trail during a fall inspection tour in 1940. Whether the short ragweed of

southern Florida (south half) should be regarded as *Ambrosia elatior* or *Ambrosia monophylla* is a technical question which is only of academic interest to the allergist, since the activity of southern Florida ragweed pollen seems to be identical with that of short ragweed growing in other parts of the United States. Dog fennel (*Eupatorium capillifolium*) and the groundsel tree (*Baccharis halimifolia*) are insect-pollinated composites whose pollen may occasionally affect ragweed sensitive persons in almost any part of the state.

Certain communities on the east coast of Florida, particularly Miami Beach and Miami, have been advertised in recent years as hay fever refuges. Metzger says, "The east coast section—the nearer the beach the better—should afford freedom from symptoms to all sufferers from the pollen of ragweed." Statistical evidence on this point is not nearly as complete as it should be. The claims, which are probably true, have been based largely on the results of atmospheric sampling done in Miami during the months of August to November, 1929. On the 84 slides exposed, I found a total of only 8 granules of ragweed pollen on 1.8 square centimeter. This is the lowest total obtained anywhere in the United States east of the Continental Divide, being much less than the 205 total found the next year at Jacksonville. The findings at Miami can be accounted for by both botanical and meteorologic facts. Short ragweed does not grow on the sandy beaches or in the sterile coral outcrop, of which there are vast acreages in southern Florida. The only ragweed growing along the shore is a shrubby form of marsh elder, *Iva imbricata*, specimens of which are rare and practically nonproductive. Also and fully as important is the fact that most of the wind movement during the summer and fall is from the ocean, so that ragweed pollen from the inland gardening and farming areas is not blown to the beach. Nevertheless, it would be well worth while if several series of tests could be run over a period of years at such places as Miami Beach, Palm Beach, Daytona Beach and Jacksonville Beach.

Spiny amaranth (*Amaranthus spinosus*) and a southern species of water hemp, *Acnida cannabina*, are locally abundant in some parts of the state. I have observed the latter in great abundance (8 foot weeds) in ditches along the highway between Orlando and the east coast.

Various grasses shed small amounts of pollen throughout the year. Bermuda grass and St. Augustine grass (*Stenotaphrum secundatum*) are widely distributed. Natal grass (*Tricholaena rosea*) is abundant in the Miami area. The oaks and pecans are the chief source of tree pollen during the months of February, March and April. The trees are more abundant in the interior and northern parts of the state rather than near the coast. In southern Florida an imported tree called Australian pine (*Casuarina lepidophloia*) is planted in great numbers. It sheds a considerable amount of pollen which if active allergenically is not very toxic. The pollen of the shrub wax myrtle (*Myrica cerifera*) is a potential factor during February and March in most of Florida.

Georgia

Field Studies:

Observations at Savannah and Columbus, 1928, Decatur and Waycross, 1940, and Moultrie, 1943, by author (O.C.D.).

Combined Field and Atmospheric Studies:

Atlanta, 1929, 1943, 1944, O. C. Durham and Hal M. Davison, M.D.

Atmospheric Records:

Atlanta, summer and fall, 1929-1934, 1937, by author (O.C.D.).

St. Simons Island, 1945, O. C. Durham and B. W. Harris, M.D.

Atlanta, summer and fall, 1947, J. L. Jacobs, M.D.

Tree season, January to May.
Grass season, April to October.
Ragweed season, August to October.

Although atmospheric tests have been made in only two places in Georgia, there is ample evidence that ragweed is abundant in all parts of the state. The ragweed situation at St. Simons Island as revealed by atmospheric sampling and counting has been a real disappointment to those who had hoped that the coast of Georgia would prove to be as free of ragweed as the east coast of Florida. In Atlanta traces of ragweed pollen remained in the air until Christmas and in St. Simons Island until mid-January. Almost all of the ragweed pollen found in the air in these studies came from short ragweed and giant ragweed. Although cockleburrs grow luxuriantly in many parts of the state and shrubby marsh elder (*Iva oraria*) is found along the Atlantic Coast, neither of them produces enough pollen to be of more than minor local importance. There are no other ragweeds in the state. About 95 per cent of all fall pollen in Georgia is from ragweed, the remainder being furnished by pigweed, lamb's quarters, and spiny amaranth, none of which are regarded as of clinical importance.

Grass pollen incidence is very low at Atlanta as well as at St. Simons Island. In both places the highest incidence occurred not in spring or summer but in September and October. Dr. Davison observes that only a small proportion of hay fever cases throughout the state is specifically sensitive to grass pollen. Bermuda grass is abundant throughout the state and is the most active of the grass pollens; Johnson grass is probably a poor second. The exact source of the grass pollen appearing in the air in the late fall has not been determined.

Tree pollens appear in the air in Georgia in considerable amounts as early as January, reach a climax in St. Simons Island in March, in Atlanta in April, and are mostly gone a month later in each place, respectively. Dr. Davison emphasizes the clinical importance of elm, oak and pecan, the latter being a frequent offender in the extensive pecan-growing sections of the southern part of the state. Alder pollen is a rare offender. No one has investigated or at least reported of the clinical activity of wax myrtle pollen. In the following table the more common trees are listed in their order of pollination. The figures show comparative seasonal volumetric incidence of the tree pollens as compared with ragweed pollen in the two cities studied in 1933 and 1934.

TABLE XXXVI. POLLEN INCIDENCE IN TWO GEORGIA LOCALITIES

	ST. SIMONS ISLAND	ATLANTA
Cypress and cedar	1,318	160
Alder	17	604
Elm	28	3,450
Wax myrtle	3,455	169
Oak	2,146	2,588
Sweet gum	14	209
Sycamore	25	82
Hickory	0	245
Walnut	0	21
Ragweed	4,801	4,591

Hawaii

Field Studies:

Island group, 1943, C. T. Young, M.D., and W. R. Cook, M.D.

Combined Field and Atmospheric Studies:

Island group, 1939, L. H. Roddis, M.D.

The following abstract of Dr. Roddis' article appeared in the *Journal of Allergy*. No detailed figures for atmospheric studies were included in the abstract and it is not evident what the "count at Honolulu was 28" refers to.

"The pollens of Hawaii are discussed. The tropical plants, which are very numerous in the islands, are not common causes of hay fever since the pollens they produce are sticky, large in size, and have low toxic properties. One tree, the cycad palm, produces enormous amounts of pollen, but skin reactions have not been obtained with it. This palm is a gymnosperm, related to the forerunners of the conifers (pine).

"Pollen counts were very low because of the insular position, high precipitation, and natural barriers; the count at Honolulu was twenty-eight. Consequently, less hay fever and asthma are encountered. The pollens most frequently causing trouble were: redtop, Bermuda grass, date palm, royal palm, algarroba (*Prosopis juliflora*), sugar cane, and mango (*Mangifera indica*). Those pollens which are produced in profusion but are not easily wind-borne still cause many cases of hay fever when the trees producing them are close to the house. The hibiscus flower, the emblem of Hawaii, which is used as a decorative flower and is worn in the hair by the women, has been responsible for hay fever in several cases."

A personal communication from Dr. Tell Nelson in April, 1946, includes the following information: "Grasses are of course a constant source of trouble, as are molds and dusts and a goodly sprinkling of ragweed in certain areas of Oahu. Have not seen any around here [Warakoa, Maui]."

The only mention of seasonal incidence in available articles is as follows: sugar cane, November to January, algarroba tree, February to June.

Idaho

Field Studies:

Statewide, 1930, Robt. F. E. Stier, Guy Hollister and Thomas A. Bonser.
Observations in Boise, Caldwell, Pocatello, Rexburg, and Rigby—one-half of the southern counties, by author (O.C.D.).

Combined Field and Atmospheric Studies:

Sun Valley, June to October, inclusive, 1940, 1941, O. C. Durham, and John R. Moritz, M.D.

Atmospheric Records:

Boise, summer and fall, 1929, 1933, by author (O.C.D.).
Moscow, 1940, Jean Daubenmire.

Tree season, March and April.
Grass season, June to September.
Ragweed season, August and September.

Field observations in a number of places in southern Idaho, together with atmospheric tests at Boise, Sun Valley and Moscow, show that the principal sources of hay fever pollen in the state are sagebrush (*Artemisia tridentata*), burweed marsh elder (*Iva xanthifolia*), Russian thistle (*Salsola pestifer*) and the grasses. Of the three weeds, ragweed pollen was most abundant at Boise, sagebrush at the other two points. Stray specimens of other ragweeds than burweed marsh elder, such as poverty weed (*Iva axillaris*), western ragweed and several species of false ragweed, may be found here and there but throughout the irrigated valleys burweed marsh elder is outstanding. However, at Boise most of the ragweed pollen was from some other source, perhaps false ragweed (*Franseria acanthicarpa*). Ragweeds of any kind are practically if not entirely

absent from the dry prairies, foothills and mountains, where sagebrush is usually dominant. Two years of atmospheric testing at Sun Valley showed that the winds bring in only a trace of ragweed pollen from the distant irrigated valleys. Likewise at Moscow ragweed pollen was found only in insignificant amounts.

Evaluation of the chenopods is difficult because the atmospheric tests have all been made in or near the mountains. Very little of this type of pollen was found even at Boise. Russian thistle is abundant throughout the extensive irrigated areas in the Snake River Valley so there is quite likely some hay fever difficulty in these areas in July, August and September from Russian thistle pollen. Other *Chenopodiaceae* whose geographic distribution or productive ability is limited are greasewood (*Sarcobatus vermiculatus*), shadscale (*Atriplex canescens*), burning bush (*Kochia scoparia*) and *Bassia hirsuta*, a recently introduced annual resembling burning bush.

The grasses of the towns and farms of southern Idaho are the same as those of the middle states—bluegrass, timothy, orchard grass and redtop. Wild grasses probably shed only a small amount of pollen. Principal wild grasses noted were the wheat grasses (*Agropyron spp.*). Crested wheat grass (*Agropyron cristatum*) has been introduced and is now well established in some areas. (Noted at Pocatello.) The grass season in Moscow is given by Daubenmire as late April to late September, but in Boise there was very little grass pollen in the air after the first of July. The active season probably does not begin in southern Idaho before the middle of May.

Since most of the tree pollens of the mountainous areas are of the conifer type, the only trees that need be considered as possible sources of allergy are the shade trees of cities, towns and farmyards. The principal ones I have noted are American elm, Chinese elm, box elder, ash, and cottonwood.

Illinois

Field Studies:

Statewide including all cities of 10,000 population and more, 75 of the 102 counties, 1933, by author (O.C.D.).

Chicago, 1926, Harry L. Huber, M.D.

Combined Field and Atmospheric Studies:

Chicago, 1925, K. K. Koessler, M.D., and O. C. Durham.

Chicago and suburbs, 1933, S. M. Feinberg, M.D., and O. C. Durham.

Atmospheric Records:

Chicago, summer and fall, 1928, Siegfried Maurer, M.D.

Chicago, 1929-1946, by author (O.C.D.).

Chicago, 1947, T. B. Bernstein, M.D.

Bloomington, 1934, 1935, 1937, Gerald M. Cline, M.D., and O. C. Durham.

Decatur, summer and fall, 1947, Helen C. Hayden, M.D.

Grayslake, 1943, 1944, Stanley Anderson, M.D.

North Chicago, 1931-1934, by author (O.C.D.).

Peoria, 1934, Mildred E. Merkle, M.D.

Peoria, 1947, Leonard H. Harris, M.D.

Rockford, summer and fall, 1932-1944, John R. Porter, M.D.

Rockford, summer and fall, 1946, 1947, Department of Public Health, N. O. Gunder son, M.D.

Rock Island, summer and fall, 1940-1942, files of author (O.C.D.).

Streator, summer and fall, 1936, files of author (O.C.D.).

East St. Louis, see St. Louis, Missouri.

Tree season, March to May.

Grass season, mid-May to mid-July.

Ragweed season, August and September.

Ragweed pollen is more important in Illinois as a cause of hay fever than that of all other wind-pollinated plants taken together. From 95 per cent to 98 per cent of all the pollen in the air during the late summer and fall in all places so far tested is that of the ragweeds, and a very large but undetermined proportion of this is from short (or common) ragweed. Giant ragweed contributes almost all of the remainder in the north half of the state. In the south half of the state southern ragweed (*Ambrosia bidentata*) is more abundant than giant ragweed, locally sometimes even more abundant than short ragweed. Burweed marsh elder (*Iva xanthifolia*) is very abundant in Chicago, but its pollen constitutes only a small proportion of that found in the air in the city. This plant is found in limited amounts at Peoria and a few other points along the Illinois River but is not abundant enough to be even a local factor outside of the Chicago area and possibly Peoria. Rough marsh elder (*Iva ciliata*) is found along the Mississippi from East St. Louis southward but is probably relatively unimportant anywhere. Only insignificant traces of western ragweed remain within the borders of the state. Cockleburs contribute insignificant amounts of the airborne ragweed content of the air.

The chenopod-amaranth group of plants is represented in the state by large acreages of pigweed and lamb's quarters, neither of which seems to be clinically important. Russian thistle is not abundant enough anywhere in the state except in the Calumet region of Chicago to be even a local factor in allergy. Burning bush (*Kochia scoparia*) has in the last ten years invaded Chicago where it is now a rival of ragweed in much of the central south side. Western water hemp is plentiful in the stock yards area in Chicago and is particularly abundant in the vicinity of East St. Louis, in which area heavy atmospheric contamination with western water hemp pollen is sometimes encountered. The pollen is evidently not extremely toxic. Another species of water hemp, *Acnida tuberculata*, is found in northern Illinois but not in effective amounts. English plantain pollen is rare in the air in Chicago and is probably not a factor in the area. It is not mentioned in Feinberg's summary of the active pollens of Chicago. Red sorrel (*Rumex acetosella*) sheds pollen at the same time as the grasses. A concentration as high as 100 granules per cubic yard of air was once encountered, concentrations of 50 granules per cubic yard having been noted two or three times. The pollen is almost entirely inactive as an allergen.

Bluegrass, timothy, orchard grass and redtop are the important hay fever grasses found throughout the state. In Northern Illinois, Canada bluegrass (*Poa compressa*) may be ranked in importance with the above named grasses. In the very southern tip of the state Bermuda grass is common. Corn pollen is a possible source of local exposure on farms.

Tree pollens of numerous kinds are likely to reach large concentrations in the early spring in any part of the state. Oak and elm seem to be the most common offenders. Other potential but comparatively unimportant trees are cottonwood, ash, maple, walnut, hickory, and tree of heaven.

Indiana

Field Studies:

Statewide observations including all larger centers of population, 1929, by author (C.D.).

Combined Field and Atmospheric Studies:

Indianapolis, 1928, by author (O.C.D.).

Atmospheric Records:

Cicero, summer and fall, 1930, by author (O.C.D.).

Indianapolis, summer and fall, 1926, Thurman B. Rice, M.D.

Indianapolis, 1928-1933, 1937-1944, by author (O.C.D.).

Indianapolis, 1936, 1937, 1947, C. B. Bohner, M.D.

Indianapolis, summer and fall, 1946, 1947, State Board of Health, J. W. Jackson, M.D.

East Chicago and Whiting, see Chicago.

Tree season, March to May.

Grass season, mid-May to mid-July.

Ragweed season, August and September.

From 95 per cent to 98 per cent of all the pollen in the air during the late summer and fall in Indianapolis is that of the ragweeds, and a very large proportion of this from short (or common) ragweed. Giant ragweed contributes almost all of the remainder. These proportions are quite likely maintained throughout the state, with the following local exceptions. Southern ragweed (*Ambrosia tridentata*) and rough marsh elder (*Iva ciliata*) are found in the southwest corner of the state. Whether they are abundant enough to be active factors has not been determined statistically. Burweed marsh elder (*Iva xanthifolia*) is fully as common as giant ragweed in the vicinity of Gary, but is not found elsewhere in the state. Cockleburs contribute insignificant amounts of the air-borne ragweed pollen content of the air. Annual sage is conspicuous in Indianapolis but air concentrations are very low as compared with ragweed. The season is parallel with ragweed.

The chenopod-amaranth group of plants is represented by large acreages of pigweed and lamb's quarters, neither of which seems to be clinically important. Russian thistle is found in fairly large quantities in the sandy soil near Lake Michigan but not elsewhere except as stray specimens. English plantain is a possible source of pollen but a very unlikely cause of hay fever in any part of the state. Red sorrel (*Rumex acetosella*) is very productive during the grass pollen season but the pollen is almost entirely inactive as an allergen. Hemp (*Cannabis sativa*) has been found in a few large patches in Indianapolis but only traces of the pollen have appeared on downtown test slides.

Bluegrass, timothy, orchard grass and redtop are the important hay fever grasses found throughout the state. In central and northern Indiana, Canada bluegrass (*Poa compressa*) may be ranked in importance with the above grasses. Along the Ohio River, Bermuda grass may be found in fairly large quantities. Corn pollen is a possible source of local exposure on farms.

Tree pollens of numerous kinds are likely to reach large concentrations in the early spring in any part of the state. Oak and elm seem to be the most common offenders. Other potential but comparatively unimportant trees are cottonwood, ash, maple, walnut, hickory, tree of heaven, and beech.

Iowa

Field Studies:

Statewide observations including Ames, Cedar Rapids, Clinton, Council Bluffs, Des Moines, Dubuque, Dunlap, Estherville, Le Mars, Mason City, Sibley, Sioux City and Waterloo—36 of 99 counties, 1930-1946, by author (O.C.D.).

Combined Field and Atmospheric Studies:

Ames, 1938, 1939, Julia Cole, M.D.

Atmospheric Records:

Des Moines, summer and fall, 1940-1944, by author (O.C.D.).

Des Moines, summer and fall, 1945 (author's file).

Iowa City, summer and fall, 1928-1930, Zella White Stewart, M.D.

Council Bluffs, see Omaha, Nebraska.

Tree season, March to May.

Grass season, May to July.

Chenopod season, July to September.

Hemp season, July to September.

Ragweed season, August and September.

The ragweeds are easily the outstanding hay fever hazard of the state as a whole. Short ragweed and giant ragweed are found throughout the state, the former being the source of the greater part of the ragweed pollen found on atmospheric slides. Burweed marsh elder (*Iva xanthifolia*) is as conspicuous as giant ragweed in the first one or two tiers of counties bordering the Mississippi River and in the southwestern part of the state. Cockleburrs are everywhere present in rich corn land but the output of pollen is extremely small. Western ragweed has been eradicated from all cultivated land and is not a hay fever factor in Iowa. Prairie sage and annual sage are present in very small amounts anywhere in the state.

The Chenopod-amaranth family is well represented, particularly in the west and southwest parts of Iowa. Russian thistle is not very abundant anywhere in Iowa, probably not enough to cause symptoms. Burning bush is increasing its range, traveling from west to east. It is a very conspicuous plant in all the Mississippi River counties. It is abundant in Des Moines and fairly common in the farmlands of the southwest quarter of the state. The aerial incidence of burning bush pollen in Des Moines has reached a maximum of 124 granules per cubic yard of air. This figure is comparable with records for Nebraska towns and cities along the Platte and North Platte rivers. The most important amaranth in Iowa is western water hemp (*Acnida tamariscina*). This is another Mississippi Valley weed most common in the tier of counties adjacent to the river but scattered more or less over the state. Pollen production is abundant at Omaha—maximum concentration 528 pollen grains per cubic yard of air. Similar records could probably be obtained at Sioux City and in many of the southwest counties. Appreciable amounts of this type of pollen are found at Des Moines. Pigweed and lamb's quarters are common field and garden weeds but their output of pollen is far less than that of western water hemp.

Hemp (*Cannabis sativa*), popularly known as marihuana, is another typical and conspicuous weed of western Iowa. Like several of the above named weeds it is increasingly abundant in the Mississippi Valley counties but is scattered generally throughout the state. Atmospheric incidence of the pollen is almost as great at Des Moines as in the Council Bluffs-Omaha area where hemp pollen sometimes produces a volume about 15 per cent as great as ragweed. The pollen is decidedly toxic. A related plant, Japanese hop, has very local distribution but should be regarded as a potential factor wherever found.

English plantain is present in waste places and on lawns but it is probably not a very important factor anywhere in the state. Red sorrel (*Rumex acetosella*) is common everywhere in Iowa and produces fairly large amounts of pollen. However, its toxicity is very low.

The principal hay fever grasses of Iowa are bluegrass, timothy, orchard grass, redtop and Canada bluegrass. Corn pollen is effective only on those directly exposed to corn while in tassel.

Elms are the favorite trees for planting throughout the state. The distribution of such trees as oak, birch, walnut, and hickory is limited. Cottonwood and box elder are common.

Kansas

Field Studies:

Statewide observations including Arkansas City, Beloit, Dodge City, Downs, Emporia, Fort Scott, Galena, Garden City, Great Bend, Hutchinson, Independence, Junction City,

Kansas City, Kingman, Lawrence, Liberal, Manhattan, Newton, Pratt, Topeka, Wichita, and Winfield—63 of 105 counties, 1923-1947, by author (O.C.D.).
 Manhattan, 1933, Elsa Horn.

Combined Field and Atmospheric Studies:

Wichita, 1929-1933, by author (O.C.D.).
 Goodland, 1944-1947, D. D. Vermillion, M.D., and O. C. Durham.
 Kansas City (air data Kansas City, Missouri), 1923-1925, by author (O.C.D.).

Tree season, late February to May.

Grass season, May to July.

Chenopod-amaranth season, July to September.

Ragweed season, August and September.

Sagebrush season, August and September.

The ragweeds are the most important source of hay fever pollen in the eastern half of Kansas, and decreasingly abundant in the western half. Most of the ragweed pollen in eastern Kansas comes from short ragweed and giant ragweed. Rough marsh elder is found locally in moist land in the same area, but its total contribution is certainly small. In the southeast corner of the state southern ragweed (*Ambrosia bidentata*), and in the extreme northeast corner burweed marsh elder (*Iva xanthifolia*) produce insignificant amounts of pollen. This latter plant is the principal ragweed of western Kansas. Western ragweed is common along roadsides in the southwestern part of the state, but is rare in the northwestern counties. A species of false ragweed, *Franseria tomentosa*, is also present in the same area, and is even less important. At Goodland, in the northeast corner of Kansas and in the center of a large wheat raising area, the ragweed pollen found in the air is mostly that of burweed marsh elder—season of 1946, 98 per cent. This makes it easy to assess the total contribution of all other ragweeds of the area. It may be assumed until more atmospheric tests in the Dust Bowl area prove otherwise that conditions at Goodland are typical of those of most of the northwestern part of Kansas and adjacent parts of Colorado and Nebraska. Dr. D. D. Vermillion of Goodland reports that in his practice—patients from a hundred mile radius—he seldom finds local hay fever sufferers sensitive to ragweed pollen of any kind. Since the air contains appreciable amounts of burweed marsh elder pollen (index, 23) there seems to be only one logical conclusion, namely, that burweed marsh elder pollen is not very toxic, or at least is a poor sensitizer.

Sagebrush (*Artemisia*) pollen of any sort is not a hay fever factor at either Kansas City, Wichita, or Goodland, but along the rivers of western Kansas, including the Arkansas River, and in the sand hills of the southwest counties, sand sagebrush (*A. filifolia*) is abundant. This would be a good region to test the incidence and toxicity of sand sagebrush pollen, but the task remains undone to the date of the writing of this paragraph. Prairie sage is common locally in virgin soil throughout, but is not a good producer of pollen.

The chenopod-amaranth group is well represented in the hay fever flora of Kansas. Russian thistle (*Salsola pestifer*), the worst offender in the group, is common and frequently abundant in wheat land and waste places in the western half of the state. Along the Arkansas River the Russian thistle belt begins abruptly at Hutchinson and continues far beyond the Colorado border. A similar plant of the same family, burning bush (*Kochia scoparia*), or koehia, has in recent years invaded Kansas from the northwest. It is now common in most towns in the state and disputes land rights with Russian thistle, particularly during seasons of more than average rainfall. It is also common in the Kaw Valley—Junction City to Kansas City—and along the Missouri River in the northeast corner of

the state. In Kansas City I have encountered specimens 8 feet high. The only important amaranths as far as acreage and production are concerned are western water hemp (*Achida tamariscina*) and Torrey's amaranth (*Amaranthus torreyi*). The former is very abundant in the valleys of the Missouri, Arkansas and Kaw rivers, and common in moist places in the east two-thirds of the state. The latter is confined to the southwest segment edged by the Arkansas River. The all-time maximum of atmospheric incidence of western water hemp pollen was recorded at Omaha, Nebraska, but the Wichita figure of 480 granules per cubic yard of air is nearly as high. Pigweed and lamb's quarters are common field and garden weeds but their output of pollen is far less than that of western water hemp.

Hemp (*Cannabis sativa*), popularly known as marihuana, is found in any important quantity only in the northeast corner of the state—Kaw River Valley and Missouri River Valley. English plantain is present in waste places and lawns in the eastern half of the state but the exposure of sensitive patients to the pollen is strictly local.

The principal hay fever grasses of northern and northeastern Kansas are bluegrass, timothy, orchard grass and redtop. Bermuda grass is now the principal pasture grass in the southern counties. Corn pollen is effective only on those directly exposed to corn while in tassel. The wild grasses of western Kansas produce only meager amounts of pollen.

Trees are of minor significance in the west half of Kansas. Elm and cottonwood are found along streams throughout the state. In eastern Kansas the variety of trees is greater with some oak, hickory and walnut, but specific tree pollen allergy is rare.

Kentucky

Field Studies:

Observations at Covington, Frankfort, Hopkinsville, Louisville, Paducah and in the western counties, by author (O.C.D.).

Atmospheric Records:

Louisville, summer and fall, 1930-1933, 1940, by author (O.C.D.).
Covington, see Cincinnati, Ohio.

Tree season, February to May.

Grass season, May to July.

Ragweed season, August and September.

The relative importance of ragweed pollen as compared with other air-borne pollens in Kentucky may be easily judged by the fact that ragweed pollen constitutes 95 per cent of the air content during late summer and fall at Louisville and Covington (Cincinnati figures). Most of this atmospheric load comes from short ragweed and giant ragweed. The only other ragweeds of the state are southern ragweed (*Ambrosia bidentata*) found occasionally in the extreme western counties, rough marsh elder (*Iva ciliata*) along the Ohio River and cocklebur in all cultivated and waste land. Annual sage is conspicuous at Louisville, Covington, Lexington, and most other large towns and cities. The pollen of this species may be an occasional cross-reactor with ragweed but hardly a specific sensitizer. Pigweed, lamb's quarters, and spiny amaranth are present throughout, but unimportant as sources of air-borne allergens.

Bluegrass and timothy are the dominant grasses throughout the state, but along the south edge there are considerable amounts of Bermuda grass and Johnson grass.

The various native trees, of which oak and elm are the heaviest producers, are plentiful throughout the state, but are of decidedly minor importance in allergy.

Louisiana

Field Studies:

New Orleans, 1930, W. T. Penfound, Ph.D., and B. G. Efron, M.D.
 New Orleans, 1944, W. T. Penfound, Ph.D.
 New Orleans, 1934, N. Thiberge, M.D.
 Observations in Shreveport and New Orleans by author (O.C.D.).

Combined Field and Atmospheric Studies:

New Orleans, 1916-1922, Wm. Scheppegegrell, M.D.

Atmospheric Records:

New Orleans, summer and fall, 1929-1933, 1937, 1940, by author (O.C.D.).
 Tallulah, see Vicksburg, Mississippi.

Upper Air Tests:

Tallulah, 1923, Wm. Scheppegegrell, M.D.
 New Orleans, 1940, by author (O.C.D.).

Tree season, January to May.

Grass season, April to December.

Ragweed season, Gulf area, extreme limits, August to December; active September and October; northern area September and October.

The ragweeds of Louisiana are giant ragweed, rough marsh elder (*Iva ciliata*), short ragweed, southern ragweed, western ragweed, cocklebur and shrubby marsh elder (*Iva oraria*). In northern Louisiana away from the Mississippi River short ragweed and giant ragweed are most important with southern ragweed a minor local factor. In New Orleans and along the Mississippi River northward rough marsh elder and giant ragweed are regarded as of equal and outstanding importance. Short ragweed seems to be crowded out of the rich alluvial soil of the delta and river bottoms. Eighty-five per cent of the pollen in the air in New Orleans during the summer and fall is from ragweed, about 10 per cent from composites and most of the remainder from fall grasses. Dog fennel (*Eupatorium capillifolium*) is the most likely source of the air-borne composite pollen noted above, though *Parthenium hysterophorus* may furnish a small share. Neither plant is basically wind-pollinated. If the situation in northeast Louisiana may be judged from the atmospheric finding at Vicksburg, Mississippi, somewhat over 80 per cent of the fall pollens are from ragweed and 10 per cent from fall blooming elm.

The chenopods and amaranths, such as pigweed, lamb's quarters and Palmer's amaranth, are not abundant enough anywhere in the state to be considered more than very minor possible allergenic factors.

Bermuda grass with its long season of bloom is the leading offender among the grasses throughout the state with Johnson grass a poor second. In New Orleans the bull grasses (*Paspalum spp.*) are abundant but are probably not heavy producers of pollen. Goose grass (*Elusine indica*) and crab grass (*Syntherisma fimbriatum*) are mentioned in the survey of Penfound, Efron and Morrison along with smut grass (*Sporobolus indicus*) as being widely distributed in New Orleans.

Air-borne tree pollen is plentiful throughout the winter and spring in all parts of Louisiana. A personal communication from Dr. V. J. Derbes of New Orleans lists elm, oak and pecan as important hay fever trees with cypress and maple of secondary importance. For the state as a whole the oaks are probably

the source of the most air-borne tree pollen. Live oak (*Quercus virginiana*) is said to be found throughout the state. Elm pollen encountered in the fall during the ragweed season is small in amount and not encountered in the Gulf area. Oak, sweet gum and cottonwood are the most conspicuous wind-pollinated trees in the Shreveport area aside from the conifers.

Maine

Field Studies:

Statewide evaluation of ragweed hay fever hazards, 1876, Morrill Wyman, M.D.
Statewide, 1936, Jay N. Fishbein, M.D.

Atmospheric Records:

Tests made in 18 cities and villages between 1935 and 1940, summer and fall, C. B. Sylvester, M.D., and O. C. Durham, with collaboration of Maine State Board of Health.
Tree season, April and May.
Grass season, May to July.
Ragweed season, August and September.

More than 70 years ago short ragweed had invaded a coastal strip of farm land in Maine 50 miles wide. Since that time as forests have gradually given way to fields and vacation resorts the ragweeds have continued their northward march. Considerable effort has been made to keep ragweeds out of Mount Desert Island (now Acadia National Park), as well as the mountain summer resorts, but the efforts have not been entirely successful. Because of the restricted acreage of farm land and the comparatively short growing season for ragweed the plants do not become as luxuriant and productive as in the Mississippi Valley or even in the middle Atlantic states. Giant ragweed is rare in Maine. Shrubby marsh elder (*Iva oraria*) may be found in brackish water along the coast but its output of pollen is small. Cocklebur is of no importance. Aroostook County has yielded the best record for Maine and for New England as a whole but visitors to the region find ragweed growing in the potato fields. Whether the Sylvester records were made during typical seasons or not there is no way of knowing. The resort regions of the Rangeley Lake and Moosehead Lake areas are also quite good but the record at Kinco, though probably not typical, proves that some ragweed is found in the region. Neither the chenopods or wormwoods (*Artemisia spp.*) furnishes more than an occasional stray grain of air-borne pollen.

The grass pollens have not been evaluated in New England but are no doubt as important as in Massachusetts where grass hay fever is common. The grasses are the same as farther south, bluegrass and timothy being most important. Of the wild grasses wheat grasses (*Agropyron spp.*) are probably of slight importance. Much of the forests consists of conifers. Among the deciduous trees elms, alders, oaks and birches are the most likely sources of pollen.

Maryland

Field Studies:

Baltimore, 1926, by author (O.C.D.).

Combined Field and Atmospheric Studies:

Baltimore, 1929, Paul Acquarone, Ph.D., and Leslie N. Gay, M.D.
Baltimore, 1930, P. M. Patterson and Leslie N. Gay, M.D.
Baltimore, summer and fall, 1931, Harry B. Wilmer, M.D., and Herbert M. Cobe, Ph.D.

Atmospheric Records:

Baltimore, summer and fall, 1938-1941, H. M. Bubert, M.D., and S. Rosenberg, M.D.
Takoma Park, see District of Columbia.

Tree season, March to May.
 Grass season, May to July.
 Plantain season, May to July.
 Ragweed season, August and September.

Gay and his associates in their observation of the seasonal incidence of hay fever pollens in Baltimore found conditions there to be essentially the same as those reported earlier by Bernton for the District of Columbia, ragweed pollen constituting almost 100 per cent of all fall pollen. In this study orchard grass was emphasized as being a very heavy producer. Sweet vernal grass is responsible for opening the grass pollen season at an earlier date than in areas where this grass is not present. English plantain pollen is found in Baltimore in considerable quantities all through the grass season and as in other places in small amounts all through the summer. The principal trees, as far as production is concerned, during the two-year study were oak, hickory, poplar, and elm.

Massachusetts

Field Studies:

Statewide evaluation of ragweed hay fever hazards, 1876, Morrill Wyman, M.D.
 Statewide, 1936, Jay N. Fishbein, M.D.
 Statewide, 1947, I. Chandler Walker, M.D.
 Observations in 11 of 14 counties, by author (O.C.D.).

Combined Field and Atmospheric Studies:

Boston, 1930, 1931, F. M. Rackemann, M.D., and L. B. Smith, Ph.D.
 Boston, Newton Center, Winchester, Worcester, 1940, Henry N. Pratt, M.D., and associates.

Atmospheric Records:

Boston, summer and fall, 1929-1933, 1938-1944, by author (O.C.D.).
 Boston, 1937, 1938, Henry N. Pratt, M.D.
 Amherst and Northampton, summer and fall, 1943, Charlotte Pratt.
 Nantucket, summer and fall, 1934, 1935, by author (O.C.D.).

Tree season, April and May (occasionally March).
 Grass season, June and July.
 Ragweed season, August and September.

In Boston Pratt found that "the weed pollens consisted of ragweed (92 per cent), goldenrod (4 per cent), cocklebur (3.2 per cent) and wormwood (0.8 per cent). This bears out the clinical observation of the overwhelming consequence of ragweed in fall hay fever." There is no marked difference in the findings in other cities of Massachusetts where atmospheric tests have been made. Nantucket Island has long been advertised and patronized as a ragweed hay fever resort but as early as 1876 Dr. Wyman discounted these claims. During the same season one may now find advertising in high-class journals claiming that there is "no hay fever" in Nantucket, and local island newspaper stories saying that "over 39 tons of ragweed were destroyed this year under the campaign waged by the Civic League, augmented by the appropriation of \$500 made by the town to help rid the island of the pest. Thirty-nine tons is a lot of ragweed, no mistake, and it was all taken to the town dump and burned. But there is need for more work next year, as several places could not be cleaned up this year." See ragweed index for Nantucket, page 525.

The approximate performance of red sorrel (*Rumex acetosella*) and English plantain in central and western Massachusetts may be inferred from the records from New York City where a small amount of red sorrel pollen is found in late May and June, also a small amount of plantain from middle May until the end

of September. Neither of these pollens is evidently abundant in eastern Massachusetts, since Pratt records no weed pollen at any time in June and only negligible amounts in July. The role of English plantain in the New England area has probably been greatly overemphasized. Red sorrel is a very rare cause of inhalant allergy any place in the United States.

Quoting from Pratt's Boston survey, "There are five common grasses in New England: June, orchard, sweet vernal, red top, and timothy. The pollens of these grasses and of plantain are very difficult to differentiate, and therefore no effort was made to separate them. Furthermore Rackemann and Wagner have shown by desensitization of passively sensitized skin sites that although no one of the three commonest grasses (timothy, orchard and red top) invariably desensitizes to the two others, crossed reactions between the different species are very common."

Of the tree season Pratt says, "Among the trees, elm, birch, and oak (pollinating in the order listed) were by far the most abundant pollinators, and are therefore probably the most important clinically. There were moderate amounts of poplar and maple pollen and a little alder, ash, and beech. Pine pollen frequently appeared on the slides in fairly large amounts, but since pine pollen contains no atopic excitant, it was omitted from the charts and calculations. At two stations where linden trees were in the neighborhood, a small quantity of pollen was recovered in July, but Linden is a flowering tree and is not generally considered to be a cause of hay fever or asthma. It, too, was omitted from the charts. Occasional grains of unidentified pollen were also disregarded."

Michigan

Field Studies:

Statewide evaluation of ragweed hay fever hazards, 1876, Morrill Wyman, M.D.

Field observations in Detroit, Battle Creek, Sault Ste. Marie, all counties bordering Lake Michigan in both the upper and lower peninsulas, and the Keweenaw Peninsula, by author (O.C.D.).

Combined Field and Atmospheric Studies:

Detroit, 1931, George Waldbott, M.D., and W. C. Steere.

Atmospheric Records:

Statewide, daily tests during summer and fall in more than 50 cities and villages scattered evenly over the state, 1940-1947, Michigan Department of Health, B. H. Grigsby. For list of cities see ragweed index, page 525.

Alpena, summer and fall, 1935, by author (O.C.D.).

Ann Arbor, summer and fall, 1928, D. M. Cowie, M.D.

Ann Arbor, 1947, John M. Sheldon, M.D.

Bay City, 1929-1931, C. L. Hess, M.D.

Detroit, summer and fall, 1928, Richard McKean, M.D.

Detroit, summer and fall, 1930-1933, 1935, 1937-1940, by author (O.C.D.).

Detroit, 1947, Sidney Friedlaender, M.D. and A. S. Friedlaender, M.D.

Flint, summer and fall, 1929, B. A. Credille, M.D.

Frankfort, summer and fall, 1934, 1935, by author (O.C.D.).

Isle Royale, summer and fall, 1934, Nellie L. Brown, and O. C. Durham.

Mackinac Island, summer and fall, 1929, Siegfried Maurer, M.D.

Marquette, summer and fall, 1934, 1935, by author (O.C.D.).

Petoskey, summer and fall, 1934, 1935, by author (O.C.D.).

St. Ignace, summer and fall, 1934, 1935, by author (O.C.D.).

Sault Ste. Marie, summer and fall, 1929, 1934, 1935, by author (O.C.D.).

Tree season, mid-March to May.

Grass season, mid-May to mid-July.

Ragweed season, August and September.

Because of the long-standing reputation of northern Michigan, particularly the Upper Peninsula, as a refuge from ragweed pollen, well founded at the start but now often undeserved, it is not surprising that much effort has been expended in measuring ragweed pollen incidence throughout the area. Since 1940 the Michigan Department of Health has sponsored an annual daily check of atmospheric pollen during the fall season in more than 50 counties evenly distributed through the state. The results of this study agree with my own findings in pointing to the Keweenaw Peninsula and Sault Ste. Marie areas as the best parts of the state, except Isle Royale which is probably affected only by pollen brought from the mainland. The index ratings on page 525, except for Ann Arbor and Isle Royale, are based on my own interpretation of the state survey figures and modified in a number of places by data secured in my nationwide studies.

Ragweed pollen in Michigan comes almost wholly from short ragweed and giant ragweed in the southern part of the state and from short ragweed alone in the northern part. Burweed marsh elder is not established in any section where I have made observations. Small and relatively unproductive patches of western ragweed may be found in the Upper Peninsula. The sages (*Artemisia* spp.) are of very slight importance if any. Throughout the state biennial sage may be found in limited quantities. In the Upper Peninsula small patches of common wormwood (*A. absinthium*) and mugwort (*A. vulgaris*) are common in waste places, but the output of pollen is extremely low. Chenopods and amaranths are not important. Burning bush (*Kochia scoparia*) has invaded Detroit and may in a few years need to be reckoned with.

Waldbott noted large fields of English plantain at Grosse Pointe but does not discuss the role of this plant in his area. The important grasses of Michigan are the same as of adjoining states—bluegrass, timothy, orchard grass, redtop and Canada bluegrass. Waldbott regards wheat grass (*Agropyron repens*), known also as quack grass, as one-fourth as productive of pollen as bluegrass. This is the only wild grass in his list which can be regarded as even a minor source of air-borne pollen except barnyard grass (*Echinochloa crus-galli*), which species I have rated at the bottom of the scale.

There are still plenty of trees in Michigan, particularly in the Upper Peninsula. The heaviest producers among those active in allergy are oak, elm, aspen and birch. Ash, walnut and hickory may be occasional offenders. Maples, including box elder, and willows produce scantily.

Minnesota

Field Studies:

Statewide, 1932-1940, C. O. Rosendahl, Ph.D., A. O. Dahl, Ph.D., and R. V. Ellis, M.D. Observations in Minneapolis, Duluth and roadsides between Minneapolis and Moorhead, by author (O.C.D.).

Combined Field and Atmospheric Studies:

Minneapolis, 1940, C. O. Rosendahl, Ph.D., R. V. Ellis, M.D., and A. O. Dahl, Ph.D.

Atmospheric Records:

Minneapolis, summer and fall, 1930-1944, by author (O.C.D.).

Minneapolis, 1947, A. O. Dahl, Ph.D.

Duluth, summer and fall, 1934, 1935, 1939, 1945, by author (O.C.D.).

Moorhead, summer and fall, 1929-1933, 1937, by author (O.C.D.).

Rochester, summer and fall, 1928, C. K. Maytum, M.D.

Tower, summer and fall, 1934, 1935, by author (O.C.D.).

Tree season, April and May.

Grass season, late May to early July.

Chenopod-amaranth season, June to September.

Ragweed season, August and September.

From a clinical standpoint the ragweeds are far more important than any of the other hay fever plants of Minnesota. Short ragweed and giant ragweed predominate in all parts of the state except perhaps in the "Arrowhead" country—Cook, Lake, and St. Louis Counties, where there is still a small amount of western ragweed in the virgin soil and where short ragweed has not yet taken over. Burweed marsh elder (*Iva xanthifolia*) is more conspicuous than western ragweed, and perhaps more abundant than cocklebur. Because burweed marsh elder pollen and cocklebur pollen can be easily distinguished in atmospheric tests, their comparative incidence can be determined. At Minneapolis my figures show less than 1 per cent of burweed marsh elder pollen and less than that of cocklebur. At Moorhead the proportion is higher—about 5 per cent burweed marsh elder. The ragweed index figure for Duluth should be carefully noted because of the widespread propaganda for the city as a ragweed hay fever refuge. Half a century ago the place may have been free of ragweed but atmospheric tests at intervals during the last 20 years have shown a ragweed pollen incidence higher than many of the cities from which hay fever victims find it advisable to flee. Even with the low index figure of 6 at Tower in the wooded Arrowhead country there is still some difficulty for those with a high degree of ragweed sensitivity.

Ellis emphasizes the importance of the various sages (*Artemisia* spp.), dragon sage (*A. dracunculoides*), prairie sage (*A. ludoviciana*), mugwort (*A. vulgaris*) and pasture sage (*A. frigida*). These plants with pollen inter-reacting with that of ragweed are widely but sparingly distributed over the state, more on the western side than the eastern or northern sides. However, their output of pollen is comparatively small where atmospheric tests have been made, for example, a maximum of 90 sage pollens per cubic yard of air as against a maximum of 2,000 ragweed pollens per cubic yard of air. The disparity is even greater at Moorhead.

Dr. Ellis reports that approximately 30 per cent of the hay fever cases seen at Minnesota Students' Health Service are skin sensitive to pollens of the chenopod-amaranth group. Clinical sensitiveness is probably not as high as this figure would indicate, except in the Red River Valley where approximately 25 per cent of the pollen in the air comes from Russian thistle and burning bush (*Kochia scoparia*). My figure for Minneapolis shows less than 5 per cent. Russian thistle is doubtless the worst offender of all, but in the southern part of the state there is more pollen in the air from western water hemp (*Acnida tamariscina*) or the northern form, *Acnida tuberculata*. Hemp (*Cannabis sativa*) is not common except perhaps in the extreme southwest corner of the state. Dahl found some hemp pollen in the air in Minneapolis at one of his two stations. My Weather Bureau slides showed none.

The summer weeds, plantain and dock (including red sorrel), shed small amounts of pollen and are certainly of minor importance in the state. Bluegrass and timothy are the leading sources of air-borne grass pollen. Brome grass is planted widely but it is very questionable whether the pollen has essentially different qualities to that of the above-named grasses. The wheat grasses, or quack grasses (*Agropyron* spp.), are the most common wild grasses and the source of small amounts of air-borne pollen.

In the eastern and northern parts of the state maples, birches, poplars (including aspen), elms, ashes and oaks are all sources of more or less air-borne pollen. Oaks, elms, and poplars lead in pollen production but specific clinical sensitiveness to any of them is rare.

Mississippi

Field Studies:

Northwest corner, 1930, J. P. Henry, M.D., and A. L. Herring.
Northeast corner and city of Jackson, 1940, by author (O.C.D.).

Atmospheric Records:

Biloxi, summer and fall, 1934, by author (O.C.D.).
Vicksburg, summer and fall, 1931-1933, by author (O.C.D.).

Tree season, February to April.
Grass season, May to September.
Ragweed season, September and October.

The ragweeds of Mississippi are short ragweed, giant ragweed, southern ragweed (*Ambrosia bidentata*), and rough marsh elder. The first two are abundant throughout; southern ragweed is probably unimportant. I have seen it only in Marshall County. Rough marsh elder is plentiful all along the Mississippi Bottoms and along the Gulf. Whether the pollen is an important factor has not been determined so far either by clinical studies or atmospheric statistics. The pollen is indistinguishable for all practical purposes from that of short ragweed and giant ragweed. The great difference in the amount of ragweed pollen in the air at New Orleans and Biloxi, only 80 miles apart, is probably accounted for by the fact that Biloxi is much closer to the shore than New Orleans. Biloxi is practically ragweed pollen free when the winds are from the ocean. It has earned a local reputation as a hay fever refuge but by standards applied to the North and Northwest it would not rate very high.

Other fall weeds than the ragweeds are probably of little importance, although they constitute with the grasses nearly 20 per cent of the air content during late summer and fall. Bermuda grass and Johnson grass are the leading grasses throughout the state. For comments on other grasses in the Gulf region see surveys of the New Orleans area.

The tree pollens of the southern part of Mississippi are likely much the same as those at New Orleans. Oaks are plentiful. Pecan and elm are probably relatively important. Red elm (*Ulmus serotina*), which sheds pollen in the fall, is widely distributed. For detailed comments on the flora of the northwest part of the state one should consult the Memphis surveys.

Missouri

Field Studies:

Observations in western, central, and southern sections, including St. Louis, Kansas City, St. Joseph, Springfield, Joplin, and Hannibal—50 of 115 counties, 1916-1947, by author (O.C.D.).

Combined Field and Atmospheric Studies:

St. Louis, 1926, G. T. Moore, Ph.D., and R. V. L. LaGarde.
Kansas City, 1923-1928, W. W. Duke, M.D., and O. C. Durham.

Atmospheric Records:

Kansas City, summer and fall, 1929-1934, by author (O.C.D.).
Kansas City, summer and fall, 1936-1940, 1942-1944, Orval R. Withers, M.D., and O. C. Durham.
St. Louis, summer and fall, 1929-1935, 1937-1944, by author (O.C.D.).

Tree season, March, April and May.

Grass season, early May to mid-July.

Ragweed season, August and September.

Six kinds of ragweed are found within the state of Missouri, of which only two, short ragweed and giant ragweed, are of statewide distribution and abundant enough to rank as major causes of ragweed allergy. Burweed marsh elder (*Iva xanthifolia*) is common in the northwest corner of the state but not elsewhere. Southern ragweed (*Ambrosia bidentata*) is a common plant in the Ozark region and may be found in small amounts northward except in the northernmost one or two tiers of counties. Its contribution to the ragweed pollen crop cannot be determined with certainty. It might rank as more than a minor factor if it can be proved that the pollen has essentially different activity to that of the other ragweeds. Western ragweed and cocklebur are insignificant anywhere in the state.

The chenopod-amaranths are not very important anywhere in spite of the fact that western water hemp (*Acnida tamariscina*) is abundant in the Missouri River Bottoms from the northwest corner of the state to St. Louis. Burning bush (*Kochia scoparia*) is now a very common and conspicuous weed in Kansas City and St. Louis, but has not been reported as abundant anywhere else. Its pollen seems to lack the high toxicity of its close relative, Russian thistle. The latter is not common enough to be an active factor anywhere in the state. English plantain pollen, which is shed most abundantly during the grass season, may be a very occasional cause of difficulty. Red sorrel (*Rumex acetosella*) is the only dock species producing appreciable amounts of pollen. The toxicity is decidedly low. Hemp is important locally in the northwest corner of the state, including Kansas City.

Bluegrass and timothy are widely distributed, and are the sources of most of the air-borne grass pollen. Orchard grass and redtop are not as common as the other two but are widely distributed. Bermuda grass may be a factor in the extreme southern edge of the state.

The native trees, particularly elm and oak, are heavy producers of pollen, but the total production from any one genus does not approach that of ragweed at least in the populous parts of the state.

Montana

Field Studies:

Statewide, 1930, Robt. F. E. Stier, M.D., Guy Hollister, and Thomas A. Bonser.

Western section, 1927, A. R. Foss, M.D.

Observations in northern counties from Dakota border to Glacier National Park, also in extreme southwest corner near Yellowstone National Park, 1940, 1946, 1947, by author (O.C.D.).

Combined Field and Atmospheric Studies:

Glacier National Park, atmospheric tests made at Belton and Many Glacier, 1946, by author (O.C.D.).*

Atmospheric Records:

Miles City, summer and fall, 1929, 1933, by author (O.C.D.).

West Yellowstone, summer and fall, 1945, by author (O.C.D.).

Tree season, April and May.

Grass season, May to September.

Russian thistle season, July to mid-September.

Ragweed season, August and September.

Sagebrush season, August to early October.

*With the cooperation of National Park Service, Great Northern Railway and concessionaires.

The most important sources of hay fever pollen in Montana are, in their probable order of importance, Russian thistle, sagebrush, and burweed marsh elder (*Iva xanthifolia*). The latter is the principal ragweed in those parts of the state where I have had opportunity to observe or study air samples. It is regarded by the state botanists as a serious wheat field pest. Short ragweed, giant ragweed, western ragweed, and poverty weed (*Iva axillaris*) are minor contributors to the ragweed pollen crop. Sagebrush (*Artemisia tridentata*), pasture sage (*A. frigida*), and various forms of prairie sage are common throughout the state except in the mountainous and wooded sections. Russian thistle is common or abundant wherever farming is carried on. Burning bush is almost as conspicuous as Russian thistle, but not nearly as productive or antigenically active.

Bluegrass, timothy, and brome grass are important hay grasses. Western wheat grass (*Agropyron repens*) is widely distributed, but not a very abundant producer. As a rule grass pollens are not nearly as important in Montana as in the middle and eastern states. The trees are relatively unimportant, since trees are rare in the dry eastern part of the state and since the conifers of the mountainous section are inactive.

The unusual quality of Glacier National Park as a refuge for fall hay fever victims is shown not only by the experience of ragweed sufferers who have visited the area but by careful checks of its possible pollen hazards. No official investigator has ever reported any kind of ragweed growing in the Park. My own survey made in the summer of 1946 confirms these negative findings and shows that ragweeds are rare even in surrounding areas. Finally, tests of the air have been carried out to determine whether appreciable amounts of active pollen are blown into the Park from outside sources. During the tourist season of 1946 daily air samples were taken at Belton and Many Glacier. Analysis of these samples showed that more than 80 per cent of the time the air was entirely free of ragweed, sagebrush, and related pollens. There was only a trace at any time—occasionally one or two and once five grains of pollen per cubic yard of air. If the total amount of ragweed pollen found during the season had occurred on one day, the degree of pollen contamination would still have been negligible.

Nebraska

Field Studies:

Observations at Omaha, Lincoln, South Sioux City, Nebraska City, and valley of Platte River from Omaha to Big Springs, by author (O.C.D.).

Omaha, 1940, E. S. Maloney, M.D., and M. H. Brodkey, M.D.

Atmospheric Records:

Omaha, 1929, E. L. MacQuiddy, M.D., and O. C. Durham.

Omaha, summer and fall, 1929-1933, 1937-1942, by author (O.C.D.).

Omaha, 1932, E. S. Maloney, M.D., and O. C. Durham.

Omaha, summer and fall, 1947, E. L. MacQuiddy, M.D.

Lincoln, summer and fall, 1928, Paul Black, M.D.

North Platte, summer and fall, 1930-1933, 1936, 1937, by author (O.C.D.).

Scottsbluff, 1942, by author (O.C.D.).

Tree season, March to May.

Grass season, mid-May to mid-July.

Chenopod-amaranth season, July to mid-September.

Hemp season, August and early September.

Ragweed season, August and September.

Of the four cities in Nebraska where adequate atmospheric records have been taken, three are adjacent to the Platte River Valley, Omaha at the junction of the Platte with the Missouri River. However, the record at Omaha is much

like that of the other cities. Existing data would therefore seem to be applicable to the populous farming district of the state. Ragweeds are everywhere abundant and important with the chenopod-amaranths fully as productive as the ragweeds. In the eastern part of the state short ragweed and giant ragweed are easily dominant. In the western part of the state burweed marsh elder (*Iva xanthifolia*) furnishes most of the air-borne ragweed total—Scottsbluff 95 per cent, Omaha 6 per cent, North Platte 10 per cent. No other ragweed compares with the above three species in productive ability. Cocklebur is common in cornfields, western ragweed on the prairies of the western part of the state. Total production for either plant is very low.

The sages, including sand sagebrush of the western edge of the state and prairie sage scattered through most of the state, do not account for any appreciable amount of air-borne pollen as far as our present records go.

Russian thistle and burning bush vie with each other for possession of the soil throughout the state. The Nebraska acreage of these weeds seems to be greater than that of any of the surrounding states. At Scottsbluff, North Platte and Lincoln the bulk of the pollen of this type comes from burning bush. At Omaha and probably all points along the Missouri River western water hemp (*Acnida tamariscina*) sheds much more pollen than either Russian thistle or burning bush. It is abundant as far west as Lincoln and Grand Island. Other chenopods, like lamb's quarters and pigweeds, are of very minor importance.

The third most important weed offender at Omaha and elsewhere along the Missouri River is hemp (*Cannabis sativa*), otherwise known as marihuana. While the pollen is not shed in such great quantities as that of ragweed, it is extremely toxic. Many persons are specifically sensitive to it.

Grass pollen is abundant in the eastern third of the state and in any area where there are cultivated meadow grasses. Farther west where wild grasses are the main dependence for pasture and hay the level of atmospheric contamination by grass pollen is decidedly low. Bluegrass and timothy are standard grasses in the eastern part of the state. Brome grass is often planted along roadsides in the middle and western parts of the state. Western wheat grass is a typical wild grass of minor significance.

Large quantities of tree pollen are encountered in the eastern edge of the state with diminishing amounts toward the west. As in other midwestern states elm, ash, cottonwood and box elder are planted for shade. Oak, hickory and walnut are found along the Missouri River Valley.

Nevada

Field Studies:

Statewide, 1927, Henry Albert, M.D., and Virginia De Bell, M.D.

Observations at Las Vegas and Boulder City, and along Southern Pacific from Tecoma to Reno—9 counties of 17, by author (O.C.D.).

Combined Field and Atmospheric Studies:

Lake Mead National Recreational Area, 1947, by author (O.C.D.).*

Atmospheric Records:

Reno, summer and fall, 1933, by author (O.C.D.).

Tree season, April and May.

Grass season, June to October.

Chenopod season, July to September.

Sagebrush season, August to early October.

Ragweed season, late August and September.

*With the cooperation of National Park Service.

Records for the hay fever flora of Nevada are inadequate. Albert and De Bell rated Russian thistle as the chief offender with grasses second. Ragweeds are certainly not dominant. Note the very low ragweed index for Lake Mead, page 525. During a daylight trip by train on the Southern Pacific across the state the only ragweed observed was burweed marsh elder and this was seen only once, near Wells. Desert ragweed (*Franseria dumosa*), a spring blooming ragweed, is known to grow in the southern part of the state but it is not conspicuous in the vicinity of Las Vegas and Boulder Dam.

Albert and De Bell discount sagebrush for the Reno district, but it is certainly the most conspicuous hay fever plant on hills and deserts in the central part of the state. In irrigated valleys Russian thistle and burning bush are present, and probably abundant enough to be active.

Bermuda grass is the principal lawn grass in Boulder City. The source of grass pollen causing allergy in the Reno area was not stated in the Albert and De Bell report. The only hay fever trees noted in central Nevada were juniper, probably *Juniperus monosperma*.

New Hampshire

Field Studies:

Statewide evaluation of ragweed hay fever hazards, 1876, Morrill Wyman, M.D.

Statewide, 1936, Jay N. Fishbein, M.D.

Statewide, 1947, I. Chandler Walker, M.D.

Observations in southeast corner of state only, by author (O.C.D.).

Atmospheric Records:

Bethlehem, summer and fall, 1934, 1935, by author (O.C.D.).

Tree season, April and May.

Grass season, June and July.

Ragweed season, August and September.

No atmospheric studies have been made in New Hampshire except the one at Bethlehem in the White Mountains. For the populous districts in the southeastern part of the state the records for Boston and vicinity should be reasonably accurate (see Massachusetts discussion). Short ragweed is the chief source of difficulty. Its distribution throughout the state is much affected by the topography of the state. In the mountainous regions the acreage of cultivated land is small and thus the incidence of ragweed and ragweed pollen likewise restricted. Conditions are better toward the north end of the state, particularly on the east border near the Rangeley Lake area. Bethlehem is a fairly good place for hay fever sufferers, depending on their degree of sensitiveness and somewhat on the severity of the season.

For evaluation of the grasses and trees we quote from Pratt's survey: "There are five common grasses in New England: June, orchard, sweet vernal, redtop, and timothy. The pollens of these grasses and of plantain are very difficult to differentiate, and therefore no effort was made to separate them. Furthermore, Rackemann and Wagner have shown by desensitization of passively sensitized skin sites that although no one of the three commonest grasses (timothy, orchard and redtop) invariably desensitizes to the two others, crossed reactions between the different species are very common.

"Among the trees, elm, birch, and oak were by far the most abundant pollinators, and are, therefore, probably the most important clinically. There were moderate amounts of poplar and maple pollen and a little alder, ash, and beech. Pine pollen frequently appeared on the slides in fairly large amounts.

but since pine pollen contains no atopic excitant, it was omitted from the charts and calculations. At two stations where linden trees were in the neighborhood, a small quantity of pollen was recovered in July, but linden is a flowering tree and is not generally considered to be a cause of hay fever or asthma. It, too, was omitted from the charts. Occasional grains of unidentified pollen were also disregarded."

New Jersey

Field Studies:

Observations at Atlantic City, Trenton, New Brunswick, Newark, and Camden, by author (O.C.D.).

Atmospheric Records:

Paterson, August, 1875, ragweed tests, Elias J. Marsh, M.D.

Atlantic City, summer and fall, 1934, 1935, by author (O.C.D.)

Maplewood, New Brunswick, Teaneck, summer and fall, 1947, Verona, summer and fall, 1946, 1947, Matthew Walzer, M.D., E. H. Walzer, M.D., and Robert Chait, M.D.

Pitman, summer and fall, 1947, George I. Blumstein, M.D.

Jersey City, see Staten Island, New York.

Camden, see Philadelphia, Pennsylvania.

Tree season, March to May.

Grass season, May to mid-July.

Ragweed season, August and September.

Short ragweed and giant ragweed predominate throughout the state. For relative incidence of ragweed pollen at various points as compared with Philadelphia and New York City, see ragweed index, page 526. English plantain is relatively abundant and is probably a minor cause of allergy in all New Jersey cities. Red sorrel pollen is next in abundance among the weed pollens, but the figures are to be much discounted because of the low toxicity of the pollen. The grasses are the same as those of adjacent states—sweet vernal grass, bluegrass, timothy, orchard grass, and redtop. Hay fever trees are not abundant in the New Jersey barrens where pine predominates. In the populous centers elm, oak, and sycamore are common shade trees.

New Mexico

Field Studies:

Statewide, 1922, S. J. Watson, M.D., and C. S. Kibler, M.D.

Gallup, 1934, Alva Watry and R. W. Lamson, M.D.

Observations at Belen, Clovis, Gallup, Grants, Mountain, Sand Springs, Shiprock, Taiban, Texico, Tucumcari and Willard—14 of 31 counties, 1946, 1947, by author (O.C.D.).

Combined Field and Atmospheric Studies:

Albuquerque, 1946, 1947, W. I. Werner, M.D., W. G. Reed and E. L. Stormfels.

Atmospheric Records:

Roswell, summer and fall, 1933, by author (O.C.D.).

No general statements regarding plant abundance or seasons can be given for New Mexico. The atmospheric study at Roswell during July, August, and September showed comparable amounts of chenopod pollen (mostly Russian thistle), ragweed pollen (about half burweed marsh elder) and grass pollen. The total of all three was not large compared with middle states standards. Sagebrush was not abundant. My observations in the central and eastern parts of the state have shown Russian thistle to be the most conspicuous weed in the farming areas, with burning bush and burweed marsh elder comparatively scarce.

Some of the chenopod pollen probably comes from various saltbushes (*Atriplex* spp.). Bermuda grass is an important factor probably through the months of May to September or October.

Watry and Lamson in their report of an intensive field survey at Gallup stress the following: one-seeded juniper (*Juniperus monosperma*) pollinating in early spring, wild grasses (*Agropyron palmieri* and *Hilaria jamesii*) pollinating in the spring, various saltbushes pollinating in early summer and fall, Russian thistle in summer and sagebrush (*Artemisia tridentata*) in late fall. Juniper, Russian thistle, and sagebrush are regarded as of greatest importance.

Werner gives the seasonal incidence of hay fever pollens at Albuquerque as follows: tree season, February to April; grass season, April to October; Russian thistle season, June to September; ragweed season, September. Cottonwood and juniper are mentioned as major causes of allergy. The amount of pollen from either of these plants is roughly forty times as much as that from ragweed. The elms are also very productive, but are regarded as a minor cause of allergy. The Russian thistle and grass figures are low, but both are much higher than those for ragweed. Bermuda grass is the principal source of grass pollen. Ragweed species noted by Werner are said to include both *Ambrosia*, probably western ragweed, and "false ragweeds" (*Franseria*). Sagebrush pollen did not appear on the slides. During the period of October to January the air is practically free from all pollen. Sand sagebrush (*Artemisia filifolia*) is a conspicuous and probably important plant in the northeast corner of the state.

New York

Field Studies:

- Statewide evaluation of ragweed hay fever hazards, 1876, Morrill Wyman, M.D.
- Adirondack region, summer and fall, 1935, New York State Department of Health, B. R. Rickards.
- Observations in metropolitan area, Buffalo and Niagara Falls, by author (O.C.D.).
- New York City, 1926, Vander Veer et al., (F. H. Hodgson).

Atmospheric Records:

- Statewide, 1937-1946, 22 cities and towns, for list see ragweed index, page 526, New York State Department of Health.
- Brooklyn, summer and fall, 1936-1944, Matthew Walzer, M.D.
- Buffalo, summer and fall, 1925-1928, S. J. Parlato, M.D.
- Buffalo, summer and fall, 1929-1933, 1937-1943, by author (O.C.D.).
- Buffalo, 1944, John A. Frisch.
- Buffalo, summer and fall, 1946, 1947, Carl E. Arbesman, M.D.
- Coney Island, summer and fall, 1929, C. A. Spivacke, M.D., and O. C. Durham.
- Croton, 1946, 1947, E. H. Walzer, M.D., Jerome Sherman, M.D., Robert Chait, M.D., and Matthew Walzer, M.D.
- Fire Island, 1937, summer and fall, by author (O.C.D.).
- Fire Island, 1947, E. H. Walzer, M.D., Jerome Sherman, M.D., Robert Chait, M.D., and Matthew Walzer, M.D.
- Garden City, 1947, summer and fall, E. H. Walzer, M.D., et al.
- Hewlett, 1947, summer and fall, E. H. Walzer, M.D., et al.
- Lake Placid, summer and fall, 1934, 1935, by author (O.C.D.).
- Mineola, summer and fall, 1947, E. H. Walzer, M.D., et al.
- New York City, 1929, M. A. Ramirez, M.D.
- New York City (Manhattan), 1929-1944, by author (O.C.D.).
- New York Metropolitan Area, summer and fall:
 - Bronx, 1946, 1947, E. H. Walzer, M.D., Jerome Sherman, M.D., Robert Chait, M.D., and Matthew Walzer, M.D.
 - Brooklyn, 1945-1947, E. H. Walzer, M.D., et al.
 - Flushing, 1946, 1947, E. H. Walzer, M.D., et al.
 - Jamaica, 1947, E. H. Walzer, M.D., et al.
 - Manhattan, 1946, 1947, E. H. Walzer, M.D., et al.

- Ozone Park, 1946, E. H. Walzer, M.D., et al.
 Rockaway, 1947, E. H. Walzer, M.D., et al.
 Staten Island, 1947, E. H. Walzer, M.D., et al.
 Queens Park, 1936, Works Progress Administration.
 Rochester, summer and fall, 1940-1943, 1945-1947, Jerome Glaser, M.D.
 Saranac, summer and fall, 1935, by author (O.C.D.).
 Syracuse, summer and fall, 1933, G. C. Cooney, M.D.
 Syracuse, summer and fall, 1943, J. R. Wiseman, M.D.
 White Plains, 1947, E. H. Walzer, M.D., Jerome Sherman, M.D., Robert Chait, M.D., and Matthew Walzer, M.D.
 Yonkers, 1932, R. P. Wodehouse, Ph.D.
- Tree season, March to May.
 Grass season, mid-May to mid-July.
 Ragweed season, August and September.

The ragweeds of New York State are few in kind and numerous in quantity. Short ragweed and giant ragweed are almost the sole sources of air-borne ragweed pollen. Atmospheric concentration is heaviest in the western end of the state and lightest in the Adirondack region. Concentrations in the Catskills are not low enough for the area to be recommended as a ragweed hay fever refuge. Even in the Adirondacks very few places show a consistent low rating year after year. In Lake Placid, for example, in 1940 there were only two days with a concentration of 25 pollen grains per cubic yard of air during the summer and fall. The very next year there were 17 days when the count reached 25 or more. The index figures given in the table on page 526 are averages for each place. The old index of 93 for Buffalo was probably higher than it should be due to some unknown factor affecting the Weather Bureau slides during all the years that the Weather Bureau station was used for sampling. Subsequent studies in Buffalo have given it a lower rating. The figure assigned in the table is a compromise between the two.

Chenopods, amaranths, and sages (wormwoods) are found in small or extremely small amounts, and are probably not clinical factors anywhere in the state. English plantain, which pollinates during the grass season and afterward, is the only weed outside the ragweed group that deserves consideration. The great difficulty with testing of the pollen of this plant is to distinguish between skin reactions and clinical significance.

While grass pollen incidence is heaviest during the period noted at the beginning of this discussion, it must be remembered that grass pollen may appear in the air in toxic quantities in some localities any time during the summer and fall. Grasses involved during the regular season in New York State are those of the eastern seaboard—sweet vernal grass, bluegrass, timothy, orchard grass, and redtop. The source of grass pollen during the late summer and fall is difficult to determine, except for those who are immediately exposed to corn pollen.

The variety of wind-pollinated trees is large. In the New York City area oak, sycamore, birch, elm, ash, and hickory are the heaviest producers. Other trees of minor importance include maple, box elder, beech, walnut, paper mulberry, and tree of heaven.

North Carolina

Field Studies:

Observations in Asheville, Charlotte, Hickory, and Lenoir, by author (O.C.D.).

Combined Field and Atmospheric Studies:

Charlotte, 1933-1947, L. C. Todd, M.D.

Atmospheric Records:

Asheville, summer and fall, 1934, 1935, by author (O.C.D.).

Hatteras, summer and fall, 1934, 1935, by author (O.C.D.).

Raleigh, summer and fall, 1929-1933, by author (O.C.D.).

Upper Air Tests:

Over the Blue Ridge Mountains and the central part of the state, 1940, by author (O.C.D.).

Tree season, February to May.

Grass season, mid-May to mid-July, sometimes fall (see discussion).

Ragweed season, August and September.

The ragweeds and grasses are the chief sources of pollen in North Carolina. Short ragweed and giant ragweed are widely distributed and highly productive from Cape Hatteras to the Great Smoky Mountains. The Hatteras record is probably somewhat higher than it should be on account of the sampling station being located too close to a weed patch. The series of tests made on the ridge of the Great Smoky Mountains just over the Tennessee line give a very good idea of the relative incidence of ragweed pollen in heavily wooded sections of high altitude. They show that the upper air is contaminated during the ragweed season and that the pollen will drop down into areas where there are no weeds at all. This situation is confirmed by my own upper air tests from commercial transports flying across the state. Shrubby marsh elder (*Iva oraria*) is a minor factor, and that only in tidewater flats. Cocklebur is a very minor factor anywhere.

The role of English plantain as an allergen in North Carolina can be judged by Todd's figures averaged over 12 years. The total annual catch of this pollen was only 2 per cent as much as of ragweed.

In addition to the northern grasses, including sweet vernal grass, bluegrass, timothy, orchard grass, and redtop, which are abundant in the mountain valleys, there is considerable Bermuda grass in the warmer parts of the state. At Charlotte the average catch of grass pollen over a 12-year period was half as much as of ragweed. In 1933 grass figures were low through May and June, becoming heavier in July, and running often heavier than ragweed through September. Some grass pollen was found during the first week of October. Todd's comment follows: "The important complicating factor of the grass pollens during the ragweed season is usually overlooked. In this section of the country it is of especial importance, as the grass season carries on through the ragweed season and lasts for some time afterwards and shows a higher daily average even during the main ragweed season."

Tree pollens are very abundant throughout the Appalachian region. Oak is the most productive at Charlotte. Elm is a close second, followed by the hickory-walnut-pecan group, cedar and maple. Todd says he is "impressed with the considerable number of tree-pollen-sensitive patients."

North Dakota

Field Studies:

Statewide, 1932, R. V. Ellis, M.D., C. O. Rosendahl, Ph.D., and A. O. Dahl, Ph.D.

Observations in Fargo, Grand Forks, Minot, Devils Lake, Williston and Red River Valley, by author (O.C.D.).

Atmospheric Records:

Fargo, see Moorhead, Minnesota.

Tree season, April and May.

Grass season, June and July.

Russian thistle season, July to September.

Ragweed season, mid-July to September.

Sagebrush season, mid-August to September.

Weed production and weed pollen production are very heavy in the rich farm land of the Red River Valley—a strip of land some 30 to 40 miles wide along the extreme eastern edge of the state. Here short ragweed and burweed marsh elder (*Iva xanthifolia*) are the important ragweeds. These give a rating for Fargo (twin city with Moorhead, Minnesota) of 125 which, for all practical purposes, is as high as any place in the United States. Probably giant ragweed contributes a small amount of the total. The burweed marsh elder proportion is less than 8 per cent. Outside the Red River Valley no atmospheric testing has been done but if we may judge by the two nearest counting stations in South Dakota, Aberdeen and Mobridge, the amount of ragweed pollen in the central and western parts of North Dakota must be less than one-tenth as much as in the Red River Valley. The species involved in the drier parts of the state include those mentioned above, together with western ragweed. Poverty weed (*Iva axillaris*) is a rare form of ragweed found only in heavy alkaline soil. The sages (*Artemisia spp.*) are of minor importance in the Red River Valley and probably as important as ragweed in the middle and western sections. Pasture sage (*A. ludoviciana*) is found throughout. Sagebrush (*A. tridentata*) is common in virgin soil in the western part.

The really important sources of hay fever pollen in North Dakota are Russian thistle and burning bush. Both are widely and abundantly distributed. Judged by South Dakota statistics Russian thistle outranks burning bush in production of pollen. Since the Russian thistle pollen is known to be more toxic the relative importance of the two plants can be easily judged.

Grasses are fairly important in the Red River Valley and certainly of diminishing importance as one proceeds westward. Bluegrass is dominant in the farming area with only small amounts of timothy. Brome grass (*Bromus inermis*) and the cultivated wheat grass (*Agropyron cristatum*) are very common in farming districts.

Trees are of minor importance. Those used almost exclusively for planting in towns and farmyards are elm, cottonwood, ash, and box elder.

Ohio

Field Studies:

Observations in all principal cities throughout the state, by author (O.C.D.).

Combined Field and Atmospheric Studies:

Toledo, 1926, Karl D. Figley, M.D.

Atmospheric Records:

Akron, summer and fall, 1946, 1947, Karl D. Way, M.D.

Cincinnati, summer and fall, 1939-1944, by author (O.C.D.).

Cleveland, summer and fall, 1928, Milton B. Cohen, M.D.

Cleveland, summer and fall, 1929-1934, 1937-1941, by author (O.C.D.).

Cleveland, 1940-1944, Cleveland Health Museum, Bruno Gebhard, M.D.

Toledo, 1928, 1932, 1933, Karl D. Figley, M.D.

Youngstown, summer and fall, 1946, 1947, Samuel R. Zoss, M.D.

Tree season, March to early June.

Grass season, mid-May to mid-July.

Ragweed season, August and September.

The hay fever pollens of Ohio are essentially the same as for other states of the central Ohio-Mississippi Valley. Short ragweed and giant ragweed are the only members of the ragweed family that need be considered. Very small amounts of burweed marsh elder may be found in Toledo and Cleveland. The only form of sage is annual sage (*Artemisia annua*) which is found in Cincinnati and other communities in the southern part of the state. Its total contribution to the air content in Cincinnati is about 2 per cent of that of ragweed. English plantain and red sorrel shed their pollen during the grass season. The former is occasionally active, the latter seldom, if ever. Pigweed and lamb's quarters are widely distributed but, because of the small amount of pollen matured or low toxicity, or both, they are not regarded as of more than slight importance in allergy.

The grasses of Ohio are the same as for other northern states—bluegrass, timothy, orchard grass, redtop, and Canada bluegrass. Tree pollens are varied and abundant. Elm and oak produce the most pollen. Other trees of lesser importance include ash, maple, box elder, sycamore, walnut, and hickory. Cases of specific tree pollen sensitiveness are rare.

Oklahoma

Field Studies:

Statewide, 1926, R. M. Balyeat, M.D., and T. R. Stemen.

Statewide, 1941, Ralph Bowen, M.D.

Observations at Oklahoma City, Tulsa and in the Panhandle area, by author (O.C.D.).

Combined Field and Atmospheric Studies:

Tulsa County, Okmulgee County (cities of Okmulgee and Henryetta), Muskogee County, 1926, E. R. Denny, M.D., and G. E. Tenney.

Atmospheric Records:

Oklahoma City, 1926, 1927, 1937, 1946, R. M. Balyeat, M.D., Herbert Rinkel, M.D., and T. R. Stemen.

Oklahoma City, 1929-1933, 1937-1939, by author (O.C.D.).

Fort Sill, summer, 1941, by author (O.C.D.).

Pawhuska, 1931, E. R. Denny, M.D., and O. C. Durham.

Tulsa, 1931, E. R. Denny, M.D., and O. C. Durham.

Tree season, February to May.

Grass season, May to September.

Chenopod-amaranth season, July to early October.

Ragweed season, mid-August to mid-October.

Because of the steep gradation in rainfall from that of the Ozark region of eastern Oklahoma to the Panhandle area, the hay fever flora decreases in variety and output of pollen as one proceeds westward. No atmospheric tests have been made in eastern Oklahoma, all surveys having been confined to the middle of the state. However, it may be safely assumed that the conditions in the Panhandle are similar to those found in the Panhandle of Texas. See data for Amarillo. The ragweeds of the eastern edge of the state are short ragweed, giant ragweed, and southern ragweed (*Ambrosia bidentata*). Rough marsh elder is a very minor factor in river bottom land only. It may be found as far west as the middle of the state. Southern ragweed extends as far west as Tulsa. Its contribution to the ragweed total has not been assessed. Western ragweed is the principal ragweed of the western part of the state. It has been largely destroyed in the farming areas, but traces may be found as far east as Tulsa. The variation in index figures for the cities of central Oklahoma, page 526, is probably accounted for by the location of the sampling stations involved

more than by actual differences in average concentration year after year. Prairie sage and related species were formerly widely distributed through the central and western sections, but have now been destroyed in all farm land. In the Panhandle counties sand sagebrush (*Artemisia filifolia*) is very abundant and probably an active factor in allergy.

The amaranths and chenopods are often more abundant than ragweed in central and western Oklahoma. The amount of this type of pollen at Oklahoma City is not impressive, but along the Arkansas River and in most lowlands there is a great deal of western water hemp. Along the northern edge of the state west of Ponca City, Torrey's amaranth is common in sandy soil. It has the appearance of western water hemp, and is fully as productive. Palmer's amaranth is said to be found in south and southwest Oklahoma. Russian thistle is probably a more serious hay fever offender than any of the amaranths (including western water hemp). This tumbleweed is typical of the western part of the state. West and northwest winds are likely to blow the pollen for a considerable distance from its area of origin.

Oklahoma grasses are a mixture of northern and southern grasses, the northern grasses being bluegrass and timothy, the southern, Bermuda grass and Johnson grass. Atmospheric tests at Okmulgee revealed comparatively large amounts of grass pollen during May, moderate amounts during June and July, and appreciable amounts through September.

Tree species are varied and tree pollen is abundant in the eastern edge of the state and almost wholly absent from the western portion. In central Oklahoma sizable amounts of oak, poplar, ash, elm, and hickory pollens are obtained by air sampling.

Oregon

Field Studies:

Statewide, 1930, Robt. F. E. Stier, M.D., Guy Hollister, and Thomas A. Bonser.

Statewide, 1927, C. T. Chamberlain, M.D.

Willamette Valley, 1929, H. H. Foskett, M.D.

Observations in Portland, Pendleton, Klamath Falls and surrounding area, 1929, 1947, by author (O.C.D.).

Combined Field and Atmospheric Studies:

Olympic National Park, 1947, by author (O.C.D.).*

Crater Lake National Park, 1947, by author (O.C.D.).*

Atmospheric Records:

Portland, summer and fall, 1933, by author (O.C.D.).

Upper Air Tests:

Pendleton to Portland to Eugene and Medford, 1940, by author (O.C.D.).

Western Oregon.—

Tree season, February to April.

Grass season, late April to August.

Plantain season, May to October.

Because of the heavy rainfall of western Oregon (west of the Cascades) as compared with the very low rainfall of eastern Oregon, the discussion of the hay fever flora of the state can best be divided and presented separately. Ragweeds of any kind are so rare in western Oregon that during two whole seasons of atmospheric tests at Portland only one grain of ragweed pollen was found. One species of false ragweed, known as beach bur (*Franseria bipinnatifida*), grows

*With the cooperation of National Park Service.

on sandy beaches along the west coast but its total output of pollen is extremely small. Judging by a record obtained by Deamer at Arcata, California, some 70 miles down the coast from the southwest corner of Oregon, there might be slight atmospheric ragweed pollen contamination in the southwest corner of Oregon.

The grass pollen season is long and intense, the principal sources of this type of pollen being redtop, velvet grass (*Holcus lanatus*), orchard grass, bluegrass, perennial rye grass (*Lolium perenne*) and timothy. A number of other grasses of minor importance are listed in the literature. English plantain is probably more important in western Oregon and Washington than anywhere else in the United States. The season parallels that of the grasses. The pollen is said to be a frequent primary offender. Red sorrel (*Rumex acetosella*), a member of the dock family, is common and a good producer of pollen. The pollen is regarded as of very low toxicity.

Tree pollens are said to be more active in western Oregon than in the central states. Important trees of the Portland area include walnut, poplar, English walnut (very important locally), birch, alder, hazelnut (*Corylus californica*), oak and box elder.

There are no ragweeds in Crater Lake National Park and only a trace of sagebrush within the boundaries of the area. The 1947 atmospheric tests revealed only a few stray grains of ragweed pollen (see index, page 526) during the whole season and even fewer of sagebrush than ragweed. During the tourist season the only possible source of difficulty would seem to be the grasses. Incidence of air-borne grass pollen at the Park headquarters was less than 1 per cent as much as is encountered in western Oregon and Washington. Bracken spores, although abundant in the air during the summer, are regarded as being practically nontoxic.

Eastern Oregon.—

Tree season, March to May.

Grass season, June and July (occasionally to September).

Ragweed season, August and September.

Sagebrush season, August to October.

Sagebrush (*Artemisia tridentata*) and prairie sage (*A. ludoviciana*) are in most parts of eastern Oregon much more important than the ragweeds. Most of the small amount of ragweed comes from burweed marsh elder (*Iva xanthifolia*). In cultivated areas Russian thistle is well established and an important hay fever offender. With it are small amounts of several annual species of the salthushes (*Atriplex* spp.). Lamb's quarters and pigweeds are widely distributed in farm lands, but are probably not important plants as compared with Russian thistle.

Stier regards Kentucky bluegrass (*Poa pratensis*) as the most important grass of eastern Oregon and lists the wheat grasses as of secondary importance. Smooth brome (*Bromus inermis*) is found in waste places and cultivated soil. The total output of all grasses is low compared with grass pollen incidence in western Oregon or in the central states.

Trees are few and comparatively unimportant. Local difficulty could be caused by the pollen of birch, alder, aspen, cottonwood, and box elder.

Pennsylvania

Field Studies:

Eastern Pennsylvania, 1944, Harry L. Rogers, M.D.

Observations in Philadelphia, Pittsburgh, Altoona, Harrisburg, Washington, and Williamsport, by author (O.C.D.).

Atmospheric Records:

Altoona, summer and fall, 1944, A. H. Neidorff, M.D.
 Pittsburgh, summer and fall, 1929-1933, 1938-1944, by author (O.C.D.).
 Philadelphia, summer and fall, 1943, Harry L. Rogers, M.D.
 Pittsburgh, summer and fall, 1945-1947, Leo H. Criepp, M.D., Louis Kriendler, M.D., Theo. Aaron, M.D., and Milton Dunn, M.D.
 Philadelphia, 1927-1933, J. Alexander Clarke, Jr., M.D.
 Swarthmore, 1928, J. Alexander Clarke, Jr., M.D.
 Philadelphia, summer and fall, 1929-1933, 1938-1944, by author (O.C.D.).
 Philadelphia, 1931, H. B. Wilmer, M.D., and H. M. Cobe.
 Philadelphia, 1934, E. B. Scott, Leo H. Criepp, M.D., and M. A. Green, M.D.
 Philadelphia, 1935, 1936, J. Alexander Clarke, Jr., M.D., and A. L. Bolden, M.D.
 Philadelphia, summer and fall, 1945-1947, George I. Blumstein, M.D.
 Victor Hirsch, M.D., and Jay Spiegelman, M.D.
 Broomal, summer and fall, 1947, George I. Blumstein, M.D., Victor Hirsch, M.D., and Jay Spiegelman, M.D.
 Hatsboro, summer and fall, 1947, George I. Blumstein, M.D., Victor Hirsch, M.D., and Jay Spiegelman, M.D.

Upper Air Tests:

Over Alleghenies from Philadelphia to Williamsport and Akron, Ohio, to Philadelphia, 1939, by author (O.C.D.).

Tree season, mid-March to mid-May.

Grass season, May to mid-July.

Ragweed season, August and September.

Short ragweed is dominant throughout Pennsylvania with giant ragweed second in production and importance. There is too little pollen from cocklebur for it to be of any clinical importance. Such mountain resorts as Kane are not recommended as refuges from ragweed pollen as upper air sampling has shown heavy concentrations of ragweed pollen for several thousand feet above the Appalachian Range. A few annual sage plants may be found in the larger cities but production is probably insignificant. Clarke's count of "*Artemisia*" in 1935 and 1936 in Philadelphia can hardly be explained in the light of a total lack of these pollens in my routine Weather Bureau sampling in the same city.

Clarke's figures showed half as much grass pollen in the air as ragweed pollen. This is a very unusual record and gives an idea of the exposure of grass sensitive persons in that area. Sweet vernal grass is found east of the Alleghenies, otherwise the grasses are the same throughout—bluegrass, timothy, orchard grass, redtop. The plantain totals for Philadelphia are only a fourth as much as grass. Rogers analyzed a series of 102 persons showing positive reaction to plantain pollen and decided that only in two of these was plantain the sole cause of hay fever. He says of red sorrel: "We have seen but one person who reacted to sorrel and not to either plantain or grass. This was a weak reaction and probably the cause of a very mild hay fever."

Tuft and Blumstein found that only 1 per cent of all their hay fever cases was caused solely by tree pollens. In their list of active tree pollens the order of importance was judged to be, poplar, maple, elm, oak, sycamore, and ash. Outstanding trees in the Clarke tests were, in their order of production, sycamore, oak, poplar (cottonwood), maple, ash, elm, birch, beech, walnut, and hickory.

Rhode Island*Field Studies:*

Statewide evaluation of ragweed hay fever hazards, 1876, Morrill Wyman, M.D.
 Statewide, 1936, Jay N. Fishbein, M.D.
 Statewide, 1947, I. Chandler Walker, M.D.

Combined Field and Atmospheric Studies:

Providence, 1940, Henry N. Pratt, M.D., and associates.

Atmospheric Records:

Block Island, 1934, 1935, by author (O.C.D.).

Providence, summer and fall, 1947, Francis H. Chafee, M.D.

Tree season, April and May.

Grass season, June and July.

Ragweed season, August and September.

At least 95 per cent of the pollen in the air during the fall season in Rhode Island is from short ragweed. Giant ragweed is rare. Lamb's quarters, pigweed, and wormwood produce insignificant amounts of pollen. Plantain is not mentioned by Pratt. In the ragweed index, page 526, it will be noted that heavier ragweed pollen concentrations were encountered on Block Island than in the city of Providence. This difference is probably due to the Block Island slides being exposed much closer to sources of contamination than were the slides in Providence.

Pratt's comment on the grasses of New England, June grass, orchard grass, redtop, sweet vernal grass, and timothy, are pertinent: "The pollens of these grasses and of plantain are very difficult to differentiate, and therefore no effort was made to separate them. Furthermore, Rackemann and Wagner have shown by desensitization of passively sensitized skin sites that, although no one of the three commonest grasses (timothy, orchard and redtop) invariably desensitizes to the two others, crossed reactions between the different species are very common."

For an evaluation of the tree pollens we quote again from Pratt: "Among the trees, elm, birch, and oak were by far the most abundant pollinators, and are therefore probably the most important clinically. There were moderate amounts of poplar and maple pollen and a little alder, ash, and beech. Pine pollen frequently appeared on the slides in fairly large amounts, but since pine pollen contains no atopic excitant, it was omitted from the charts and calculations. At two stations where linden trees were in the neighborhood, a small quantity of pollen was recovered in July, but linden is a flowering tree and is not generally considered to be a cause of hay fever or asthma."

South Carolina

Field Studies:

Charleston, 1933, J. H. Hoch and J. I. Waring, M.D.

Charleston, summer and fall, 1929-1933, by author (O.C.D.).

Tree season, February to May.

Grass season, May to early August.

Ragweed season, mid-August to mid-October.

Detailed data for South Carolina are almost entirely lacking except for the vicinity of Charleston. Ragweeds are certainly the principal source of hay fever pollen, short ragweed being the leading producer. Shrubby marsh elder and cocklebur are very minor factors in the ragweed problem. However, there are two composites, essentially insect-pollinated, but occasionally sending out appreciable amounts of air-borne pollen. The groundsel tree (*Baccharis halimifolia*) is found only along the coast while dog fennel (*Eupatorium capillifolium*) is abundant inland. The grasses are decidedly southern in type with Bermuda grass the leading offender. The northern grasses are common in the mountainous sections of the state. Hoch and Waring consider the following trees

and shrubs to be most important: oak, wax myrtle (*Myrica spp.*), hackberry (*Celtis spp.*), elm and maple. Trees of possible minor importance include swamp cypress (*Taxodium distichum*), red cedar (*Juniperus spp.*), poplar, birch, beech, paper mulberry, sweet gum, sycamore, and tree of heaven.

South Dakota

Field Studies:

Statewide, 1932, R. V. Ellis, M.D., C. O. Rosendahl, Ph.D., and A. O. Dahl, Ph.D.
Observations in Black Hills area, at Aberdeen, Pierre, Rapid City, Sioux Falls and extreme southeast corner of state—24 of 69 counties, 1944, by author (O.C.D.).

Atmospheric Records:

Aberdeen, summer and fall, 1937, J. L. Calene, M.D.
Mobridge, summer and fall, 1932, G. H. Twining, M.D.
Pierre, summer and fall, 1930-1932, by author (O.C.D.).
Rapid City, summer and fall, 1936, 1937, by author (O.C.D.).
Sioux Falls, 1937, Charles A. Stern.

Tree season, March and April.
Grass season, mid-May to mid-July.
Russian thistle season, July to September.
Ragweed season, late July to September.
Sagebrush season, late August and September.

The eastern third of this state has enough rainfall to support a moderate to heavy growth of short ragweed. West of the Missouri River this important species is rare. Burweed marsh elder is common throughout but not very productive. Western ragweed is widely distributed but is not an important source of air-borne pollen. True sagebrush is not present in the eastern or central western part of the state as far as I have investigated. It is not found in the Black Hills but is present in the extreme northwest corner of the state. Prairie sage, pasture sage, and dragon sage are widely distributed, but the totals of sage pollen found in the cities listed above are not large except at Rapid City where it is certainly an important factor in hay fever.

The chenopods are everywhere conspicuous and abundant, except in the vicinity of Sioux Falls. Russian thistle is the leading offender with relatively high atmospheric incidence. Burning bush is often more abundant than Russian thistle, but usually produces much less pollen. If pigweed is important anywhere, it should be reckoned with in central South Dakota (Brule County). Here the acreage is greater and the weeds more vigorous than I have observed anywhere else. Western water hemp is locally abundant between Sioux Falls and Sioux City, Iowa, also along the Missouri River from Sioux City to Yankton. Hemp (*Cannabis sativa*) is also occasionally locally common in the extreme southeast corner of the state.

The common meadow grasses, bluegrass, and timothy, are probably as important in eastern South Dakota as they are anywhere in the Mississippi Basin. In the middle and western parts of the state contact with grass pollen is light. This prairie state is devoid of native trees except in the Black Hills area and along the streams in two or three tiers of counties on the eastern border. The favorite trees used for planting are elm, cottonwood, ash and box elder. Tree pollens are certainly a very minor factor whether considered singly or as a group.

Tennessee

Field Studies:

Memphis area, 1934, J. B. Lackey, M.D., and Alfred Goltman, M.D.
Observations in Nashville, Memphis, 1928, Knoxville, Chattanooga, 1946, Gatlinburg, 1947—25 of 95 counties, by author (O.C.D.).

Combined Field and Atmospheric Studies:

Memphis and surrounding territory, summer and fall, 1928-1930, J. P. Henry, M.D., and A. L. Herring.
Great Smoky Mountains National Park, air tests at Gatlinburg and Newfound Gap, 1947, by author (O.C.D.).*

Atmospheric Records:

Knoxville, summer and fall, 1930-1933, by author (O.C.D.).
Memphis, summer and fall, 1929-1933, 1936, 1937, 1940, by author (O.C.D.).
Nashville, summer and fall, 1937, by author (O.C.D.).
Nashville, 1939, Evangeline Bowie, M.D.
Nashville, summer and fall, 1945-1947, Edna S. Pennington, M.D.

Tree season, February to May.
Grass season, May to August.
Ragweed season, mid-August to mid-October.
Fall blooming elm season, September.
Annual sage season, September and early October.

Tennessee lies wholly within the ragweed belt. Even in the Appalachian Mountains where the acreage of short ragweed and giant ragweed is small, there is enough ragweed pollen in the upper air to cause symptoms. The best record for the state was obtained at Newfound Gap in the Great Smoky Mountains National Park. However, there are no facilities for entertaining guests in this part of the Park. In the lower altitudes on both sides of the mountain, ragweeds are everywhere present in cultivated land. Southern ragweed and rough marsh elder (*Iva ciliata*) grow sparingly in Mississippi River counties. Annual sage (*Artemisia annua*), known locally in the south as "Sweet Annie," is a typical weed of vacant lots and neglected areas in the larger southern cities. It has reached maximum development in Nashville where it is a strong rival of ragweed. Pollen production is small compared with ragweed but enough that the plant should be recognized as a locally important source of composite pollen allergy. No other weeds seem to be important in Tennessee in spite of the wide distribution of pigweed and lamb's quarters and local growths of spiny amaranth (*Amaranthus spinosus*).

The grasses of Tennessee are more southern than northern. Bermuda grass is dominant. The total amount of grass pollen in the air according to all observers is usually very small. Trees are plentiful throughout. Bowie named the following as being particularly productive: elm, hackberry, beech, oak, Osage orange, hickory and walnut. At Memphis, Lackey and Goltman listed more than 40 species of trees without evaluating any of them. The possibility of pecan pollen sensitiveness should not be overlooked. In the southeastern part of the state privet (*Ligustrum spp.*) pollen, though essentially insect-borne, is a minor cause of inhalant allergy. Red elm (*Ulmus serotina*), which sheds its pollen in the fall, often gives positive reactions on ragweed hay fever victims.

Texas*Field Studies:*

Statewide, 1929, 1935, E. D. Sellers, M.D.
South central Texas, 1930, S. W. French, M.D.
Southwest Texas, 1924, 1926, 1930-1932, I. S. Kahn, M.D.
Lower Rio Grande Valley, 1942, Ralph Bowen, M.D., and L. Irby Davis.
West Texas, 1934, E. D. Sellers, M.D.
Austin, winter, 1918, S. N. Key, M.D.
Observations at San Antonio, Austin, Fort Worth, Dallas, Dalhart and Amarillo, by author (O.C.D.).

*With the cooperation of National Park Service.

Combined Field and Atmospheric Studies:

San Antonio and surrounding area, 1944, F. W. Bieberdorf and Maj. S. F. Hampton.

Atmospheric Records:

Fort Worth, 1929-1931, S. Hulsey.
 Dallas, summer and fall, 1945-1947, J. H. Black, M.D.
 Dallas, summer and fall, 1929, J. H. Black, M.D., and O. C. Durham.
 Amarillo, summer and fall, 1931-1933, by author (O.C.D.).
 Dallas, 1929-1933, 1937, by author (O.C.D.).
 El Paso, summer and fall, 1929, by author (O.C.D.).
 Brownsville, summer and fall, 1931-1933, by author (O.C.D.).
 Corpus Christi, summer and fall, 1934, by author (O.C.D.).
 Dallas, summer and fall, 1929-1933, 1937, by author (O.C.D.).
 Fort Worth, summer and fall, 1928, T. C. Terrell, M.D.
 Dallas, 1928-1932, J. H. Black, M.D.
 Houston, summer and fall, 1928, D. H. Hotchkiss, M.D.
 Houston, summer and fall, 1930-1933, by author (O.C.D.).
 Galveston, summer and fall, 1934, 1935, by author (O.C.D.).
 San Antonio, 1928, 1929, I. S. Kahn, M.D.

Texas—North Central Area.—

Tree season, January to April.
 Grass season, April to September.
 Ragweed season, September and October.
 Scrub elm season, late August and September.

Brownsville and Lower Gulf Area.—

Tree season, January to April.
 Grass season, throughout the year.
 Amaranth season, May to October.
 Ragweed season, June to October.

Ragweeds and ragweed pollen are very abundant in east and central Texas and in the vicinity of Houston and Galveston. Atmospheric concentrations decrease as one proceeds west and northwest until they are very small at Amarillo and El Paso. Numerous ragweed species are involved. Short ragweed and giant ragweed are dominant or abundant over the east third of the state and most of the Gulf Coast. Western ragweed (*Ambrosia psilostachya*) is widely distributed in the west half of the state including the Rio Grande Valley. Production is light. Southern ragweed (*A. bidentata*) is common only in the northeast corner where it is probably a minor offender. Rough marsh elder is an important source of ragweed pollen in the Gulf area from Louisiana far beyond Houston. Narrow-leaved marsh elder (*Iva angustifolia*) is a minor producer in the central part of the state. Shrubby marsh elder is found on the immediate seacoast from Louisiana to Corpus Christi. It is of minor importance. Burweed marsh elder (*Iva xanthifolia*) grows sparingly in and south of the Panhandle area and is not an important plant anywhere in Texas. The most important species of false ragweed is slender false ragweed (*Franseria tenuifolia*), a very common plant in the vicinity of San Antonio, in fact, the dominant ragweed in this area, and more or less abundant from central Texas to El Paso. Small amounts of two other false ragweeds (*F. acanthicarpa* and *F. tomentosa*) growing in the Panhandle corner of the state are probably not important. Cocklebur grows in all fertile farm land but is of minor importance.

Dragon sage (*Artemisia dracunculoides*), or Indian hair tonic, and various species of mugwort are widely distributed in central and western Texas. Sand sagebrush (*A. filifolia*) is very abundant and conspicuous throughout the Panhandle and west Texas. In this area very few air tests have been made so no

quantitative evaluations of this type of pollen can be given. In the populous areas where atmospheric tests have been made the chenopods and amaranths have not yielded impressive amounts of pollen. However, it is known that Russian thistle is common in the west half of the state and that Palmer's amaranth is at least locally important everywhere except in the eastern section. It is probably most important in the Rio Grande Valley. Western water hemp is found in the central part of the state and Torrey's amaranth locally in the north central and northwest portions.

Bermuda grass is widely distributed throughout the state and the principal source of air-borne grass pollen. Johnson grass is of strictly secondary interest to the allergist. A large variety of wild grasses is listed for the state but very few of them are likely sources of difficulty.

The abundance and variety of trees diminish from east to west. In the central and eastern area oak, elm and poplar are heavy producers of pollen. Scrub elm (*Ulmus crassifolia*) sheds its pollen during the ragweed season, and is therefore a complicating factor in ragweed hay fever. Mountain cedar (*Juniperus sabinoidea*) of central and west Texas produces large amounts of toxic pollen throughout the winter and early spring.

Utah

Field Studies:

Statewide, 1930, Robt. F. E. Stier, M.D., Guy Hollister and Thomas A. Bonser.

Statewide, 1924, H. J. Templeton, M.D.

Statewide, 1931, J. M. Anderson, M.D.

Bryce Canyon National Park, 1947, by author (O.C.D.).*

Cedar Breaks National Monument, 1947, by author (O.C.D.).*

Observations in Brigham, Ogden, Salt Lake City and towns and roadsides on Route 89 from Salt Lake City to Kanab, also to southwest corner of state—half of the counties, by author (O.C.D.).

Combined Field and Atmospheric Studies:

Statewide, 1934, C. E. Barrett, M.D.

Zion National Park, 1947, by author (O.C.D.).*

Atmospheric Records:

Salt Lake City, summer and fall, 1930, 1933, by author (O.C.D.).

Tree season, April and May.

Grass season, May to July.

Russian thistle season, July to September.

Ragweed season, August and September.

Sagebrush season, late August to October.

The approximate dates given above are based on observations in the northern part of Utah. The native plants capable of producing allergenic pollen include the various species of sagebrush (*Artemisia* spp.), of salt-bushes (*Atriplex* spp.) and the junipers, particularly *Juniperus utahensis*. There are a number of native ragweeds, particularly western ragweed, but the amount of ragweed pollen anywhere in the state from such sources is extremely small. Even with the introduction of Russian thistle, burning bush (*Kochia scoparia*), burweed marsh elder (*Ira xanthifolia*) and false ragweed (*Franseria acanthi-carpa*) in the irrigated sections, the ragweed problem throughout the state is not a serious one. In a trip through the center of the state from north to south I found short ragweed only in one restricted area in the vicinity of Salem. Western ragweed was noted frequently in the northern and central parts but

*With the cooperation of National Park Service and Utah Parks Company.

seems to be absent from the southern end of the state. False ragweed was seen a few times, once in a heavy growth on roadsides and fields some 30 miles south of Salt Lake City. It was encountered only occasionally elsewhere. Sagebrush pollen is more important for the state as a whole but the heaviest stands of sagebrush are usually too far from centers of population for the pollen to do much damage.

In all populous areas Russian thistle is the prime offender. Its output of pollen is supplemented with that of the native saltbushes, both annual and perennial. *Bassia hirsuta* is a recently introduced member of the chenopod family. The heaviest stand I have seen is in the Bear River Game Refuge but it is found in small quantities down through the center of the state. Burning bush is abundant in Salt Lake City but not very conspicuous elsewhere.

Grass pollens are a factor in the larger cities and towns and on irrigated land. Bluegrass, orchard grass and the wheat grasses (*Agropyron spp.*) are regarded as the chief sources of air-borne grass pollen. Cottonwood and aspen trees are possible sources of pollen in cities and towns and along water courses. There are oaks in the canyons and cedars (*Juniperus spp.*) on the hills.

Vermont

Field Studies:

Statewide evaluation of ragweed hay fever hazards, 1876, Morrill Wyman, M.D.

Statewide, 1936, Jay N. Fishbein, M.D.

Statewide, 1947, I. Chandler Walker, M.D.

Observations in southeast corner only, by author (O.C.D.).

Tree season, April and May.

Grass season, May to July.

Ragweed season, August and September.

Wyman rated the area between the Green Mountains and Lake Champlain as being infested with ragweed. Unfortunately, no systematic atmospheric studies have been made anywhere in Vermont but enough has been done at Burlington by Dr. Medivetsky to prove that there is plenty of ragweed in the area. See index for Farnham, Quebec, page 527, some 40 miles north of the Vermont border. Doubtless there are some places east of the Green Mountains where ragweeds are rare or absent but it is unlikely that any of them could be rated as excellent hay fever refuges. They are too close to farming areas. The five common grasses of the eastern states are all present—sweet vernal grass, bluegrass, timothy, orchard grass, and redtop. We have no data on the performance of wind-pollinated trees except the general information in the surveys by Pratt and by Rackemann. Elm, birch and oak are doubtless the principal offenders.

Virginia

Field Studies:

Southern and western sections, 1931, Warren T. Vaughan, M.D.

Observations at Alexandria, Richmond and Norfolk, by author (O.C.D.).

Richmond, 1932, W. B. Blanton, M.D.

Combined Field and Atmospheric Studies:

Richmond, 1927-1932, Warren T. Vaughan, M.D., W. R. Graham, M.D., and R. W. Crockett.

Charlottesville, 1936, E. C. Cocke, Ph.D.

Atmospheric Records:

Alexandria, see Washington, D. C.

Tree season, February to May.

Grass season, mid-May to mid-July, sometimes later.

Ragweed season, August and September.

Short ragweed and giant ragweed are abundant throughout the state. Shrubby marsh elder (*Iva oraria*) of the immediate seacoast and cocklebur need hardly be considered because of their low output of pollen. At Charlottesville only a trace of sage (*Artemisia*) pollen was found. For Richmond, Vaughan emphasizes the following grasses: bluegrass, orchard grass and timothy. Bermuda grass is present except in the mountain areas but it is not stressed as an active source of allergy. Red sorrel and English plantain shed appreciable amounts of pollen throughout the grass season. The latter is a minor cause of allergy usually complicating grass cases, the former is of such low toxicity as to be disregarded completely. Tree pollen incidence at Richmond and at Charlottesville far exceeds that of ragweed. The principal producers aside from pine at Charlottesville are oak, paper mulberry, cedar, cypress, ash, sycamore, alder, and hickory. Elm is probably much more important in the state as a whole than would be judged from Cocke's Charlottesville records.

Washington

Field Studies:

Statewide, 1930, Robt. F. E. Stier, M.D., Guy Hollister and Thos. A. Bonser.

Statewide, 1947, James E. Stroh, M.D.

Observations at Seattle, Port Angeles and Puget Sound area, by author (O.C.D.).

Combined Field and Atmospheric Studies:

Western Washington, 1937, Philipp Schonwald, M.D.

Seattle and vicinity, 1940, 1947, James E. Stroh, M.D.

Mount Rainier National Park, air samples taken at Longmire, Paradise and White River, 1947, by author (O.C.D.).*

Olympic National Park, 1947, by author (O.C.D.).*

Atmospheric Records:

Seattle, summer and fall, 1929, 1936, by author (O.C.D.).

Spokane, summer and fall, 1933, by author (O.C.D.).

Western Washington.—

Tree season, late February to April.

Grass season, late April to mid-October.

Dock and plantain season, May to mid-October.

Because of the heavy rainfall in Washington, west of the Cascades, as compared with the very low rainfall of eastern Washington, the discussion of the hay fever flora of the state can best be divided and be presented separately. Ragweeds of any kind are so rare in western Washington that during a whole season of atmospheric tests at Seattle not a single grain of ragweed pollen was found. One species of false ragweed, known as beach bur (*Franseria bipinnatifida*), grows on sandy beaches on the west coast and the Strait of Juan de Fuca. I have not seen it in Puget Sound. The output of pollen is extremely small.

The grass pollen season is long and intense, the principal sources of this type of pollen being velvet grass (*Holcus lanatus*), orchard grass, timothy, various species of fescues (*Festuca* spp.) and redtop. A number of other grasses of minor importance are listed by Stroh. This author regards English plantain pollen as less important than grass pollen, reacting on about half as many people. It is often a primary offender. Red sorrel (*Rumex acetosella*), a member of the

*With the cooperation of National Park Service.

dock family, is common and quite productive. The pollen is regarded as of low toxicity.

Tree pollens are said to be more active in western Washington than in the central states. Important trees and shrubs mentioned by Stroh include alder (*Alnus oregona*), hazelnut (*Corylus californica* and *C. avellana*) and birch.

Bracken spores, although abundant in the air during the summer, are regarded as being practically nontoxic.

Eastern Washington.—

Tree season, March to May.

Grass season, June and July, occasionally to September.

Ragweed season, August and September.

Sagebrush season, August to October.

Sagebrush (*Artemisia tridentata*) and prairie sage (*A. ludoviciana*) are in most parts of eastern Washington much more important than the ragweeds. Most of the small amount of ragweed comes from burweed marsh elder (*Iva xanthifolia*). In cultivated areas Russian thistle is well established and an important hay fever offender. With it are small amounts of several annual species of the saltbushes (*Atriplex spp.*). Lamb's quarters and pigweeds are widely distributed in farm lands but are probably not important plants as compared with Russian thistle. Stier regards Kentucky bluegrass (*Poa pratensis*) as the most important grass of eastern Washington and lists the wheat grasses, *Agropyron inerme*, *A. Spicatum*, and *A. repens*, of secondary importance. Smooth brome (*Bromus inermis*) is found in waste places and cultivated soil. The total output of all grasses is low compared with grass pollen incidence in western Washington or in the central states. Trees are few and comparatively unimportant. Local difficulty could be caused by the pollen of birch, alder, aspen, cottonwood and box elder.

For those who wish to patronize a good ragweed hay fever refuge, western Washington, like western Oregon, offers the ultimate to be found in the United States. In fact, it would be difficult for anyone to find a place west of the Cascades where he *could* have ragweed hay fever. Recent atmospheric testing in Mount Rainier National Park and in Olympic National Park has revealed ragweed indices almost as low as would be found in mid-ocean.

West Virginia

Field Studies:

Observations at Wheeling, Clarksburg and Charleston, by author (O.C.D.).

Atmospheric Records:

White Sulphur Springs, summer and fall, 1936, by author (O.C.D.).

Tree season, March to mid-June.

Grass season, late May to mid-July.

Ragweed season, August and September.

Pollen conditions in West Virginia are probably similar to those of western Pennsylvania except for a lower acreage of weeds and lower ragweed incidence. It is unlikely that there is any place in the West Virginia mountains that could be regarded as a refuge from ragweed. Certainly the figure for White Sulphur Springs is not encouraging. The hay fever grasses are those of the adjoining northern states. Tree pollens are no doubt abundant although no one has taken the trouble to assess them. Coker's findings at Charlottesville, Virginia, are probably typical of at least the eastern side of West Virginia. Tree pollens as well as weed and grass pollens on the west side of the state should be much like those found at Cincinnati and Pittsburgh.

Wisconsin

Field Studies:

Statewide, 1936, Norman C. Fassett, M.D., Lester McGary, M.D., and Laura F. Bates. Observations in Milwaukee, Madison, Green Bay, Wisconsin Rapids, Eagle River, Superior, Door County, Bayfield County, Plum Island and many other points in the western and southern counties, by author (O.C.D.).

Combined Field and Atmospheric Studies:

Madison, 1936, Norman C. Fassett, M.D., Lester McGary, M.D., and Laura F. Bates.

Atmospheric Records:

Madison, summer and fall, 1935, 1936, 1938-1947, Wm. A. Mowry, M.D.

Milwaukee, 1935, 1936, 1946, 1947, T. L. Squier, M.D.

Milwaukee summer and fall, 1931-1933, 1935, 1938-1945, by author (O.C.D.).

Eagle River, summer and fall, 1934, 1935, by author (O.C.D.).

Plum Island, summer and fall, 1934, 1935, by author (O.C.D.).

Sheboygan, summer and fall, 1937, Wisconsin State Board of Health, Elizabeth M. Strassburger.

Tree season, April and May.

Grass season, June and July.

Ragweed season, August and September.

Ragweed conditions in southern Wisconsin are as bad as ragweed conditions can be. In the north end of the state, much of which is densely forested, there are large areas where no ragweed can be found. However, the distance between the two extremes is not great enough to insure ragweed pollen free air in the northern portion of the state. South winds carry appreciable amounts of pollen clear across the state. The Door County Peninsula has frequently been advertised as an excellent haven for hay fever sufferers. Our observations in Door County and air tests at Plum Island just beyond the end of the peninsula, show that ragweed is abundant throughout and the air badly contaminated except perhaps on days of ideal wind direction. Short ragweed and giant ragweed are dominant throughout the agricultural areas. Burweed marsh elder (*Iva xanthifolia*) is found in a few scattered places but is nowhere common enough to be a contributing factor in ragweed allergy. Western ragweed and cocklebur are also negligible.

The sages, such as tall wormwood (*Artemisia caudata*) and prairie sage (*A. ludoviciana*), have not produced more than traces of air-borne pollen in the localities where air studies have been made. The chenopods are also relatively unimportant in Wisconsin. At Madison where stray specimens of Russian thistle may be found, the total chenopod catch on the atmospheric slides has amounted to only 3 per cent as much as ragweed. In recent years burning bush has become established in Milwaukee and has attained considerable acreage. The maximum count for any one day so far has been 33 grains per cubic yard of air but it is possible the plant will in time become moderately important in the city. It may also spread to other communities.

The common northern grasses are well distributed and are as important in Wisconsin as in any of the middle states. These include bluegrass, timothy, orchard grass, redtop and Canada bluegrass.

The forest and shade trees of Wisconsin are typical of those of other north central states except that birch and alder are particularly abundant. Oak is the leading producer. Elm pollen is probably the most active allergenically.

Wyoming

Field Studies:

Statewide, 1930, Robt. F. E. Stier, M.D., Guy Hollister, and Thomas A. Bonser.
Observations in Cheyenne, Laramie, Rock Springs, Jackson Hole, Evanston, and extreme northeast corner, by author (O.C.D.).
Grand Teton National Park, 1947, by author (O.C.D.).

Combined Field and Atmospheric Studies:

Yellowstone National Park, 1940, 1941, 1947, atmospheric tests at Mammoth, Old Faithful, Canyon (see also West Yellowstone, Montana), by author (O.C.D.).*

Atmospheric Records:

Lander, summer and fall, 1933, by author (O.C.D.).
Eastern Wyoming, see records for Scottsbluff, Nebraska and Rapid City, South Dakota.
Tree season, April.
Grass season, June and July.
Russian thistle season, July to mid-September.
Ragweed season, July to mid-September.
Sagebrush season, August to early October.

The atmospheric pollen record at Lander in the west central part of the state is not necessarily typical for the eastern half of Wyoming. Records for southwestern South Dakota and northwestern Nebraska may be of some help in judging conditions in the eastern part of the state. At any rate there is considerable evidence that ragweed is an important factor even though the aerial incidence is not as great as in the Mississippi Valley. Ninety-four per cent of the ragweed pollen at Lander was from burweed marsh elder (*Iva xanthifolia*). Western ragweed and false ragweeds (*Franseria* spp.) are widely distributed but not very productive. Giant ragweed is not present in those parts of the state where I have observed. Short ragweed is rare.

Sagebrush is the most conspicuous hay fever plant throughout the state. At Lander as much sagebrush pollen was found in the air as ragweed pollen. In the northwest corner of the state where ragweeds are almost entirely absent the proportion, but not the amount, of sagebrush pollen is of course much greater.

The chenopods are important in cultivated areas, the principal species being Russian thistle and burning bush (*Kochia scoparia*). The native saltbushes are present in some places but entirely absent over large areas. In irrigated farming districts bluegrass, timothy, orchard grass and redtop are planted, also smooth brome (*Bromus inermis*). Grass pollen hay fever is probably less important than in states with more rainfall. The principal tree offenders are the poplars, including cottonwood and aspen.

Yellowstone National Park has a clean bill of health as far as ragweed is concerned but since some ragweed patients are clinically susceptible to sagebrush pollen all ragweed sufferers visiting the Park during the latter part of the tourist season should be warned to avoid close contact with sagebrush.

Canada

Alberta

Field Studies:

Province as a whole, 1937, H. C. Jamieson, M.D.
Observations in Waterton Lakes National Park, 1946, by author (O.C.D.).

*With the cooperation of National Park Service and Yellowstone Park Company.

Tree season, April.

Grass season, June.

Chenopod season, July and August.

Ragweed and sagebrush seasons, August and early September.

Jamieson has found short ragweed in Alberta only "to a slight extent in the area south of Medicine Hat." My own observation in the vicinity of Waterton Lakes National Park did not reveal ragweeds of any kind. Cocklebur is said to be present in cultivated land and poverty weed (*Iva axillaris*) in alkaline or saline soil but the ragweed pollen catch at Prince Albert was practically nothing. The only chenopod that has established itself is Russian thistle. It is regarded by Jamieson as the most important hay fever plant in the wheat country of central Alberta. This author mentions "*Artemisia*" (probably sagebrush) as growing seven feet high "on the banks of the Athabasca." Prairie sage and pasture sage are common in the southern part of the province but do not produce much pollen.

British Columbia

No pollen surveys of any kind have been made or at least published for this province. Conditions in the vicinity of Vancouver are undoubtedly very similar to those of the Puget Sound area where ragweed pollen is entirely absent from the air (see discussion for western Washington). Stray specimens of one or two species of ragweed have been reported from points farther east. Sagebrush is probably a factor in central and eastern British Columbia.

Manitoba

Field Studies:

Province as a whole, 1939, 1940, C. H. A. Walton, M.D.

Combined Field and Atmospheric Studies:

Province as a whole, including atmospheric studies in Brandon, Dauphin, Morden, Pierson, Russell, The Pas and Winnipeg, 1940, C. H. A. Walton, M.D., and Margaret G. Dudley, Ph.D.

Atmospheric Records:

Winnipeg, 1947, Margaret G. Dudley, Ph.D.

Winnipeg, summer and fall, 1930, 1933, by author (O.C.D.).

Tree season, April to June.

Grass season, June and July.

Chenopod season, July to early September.

Ragweed season, late July to early September.

Sage season, August to mid-September.

Walton and Dudley have carried on survey work in this province for a number of years, publishing meanwhile several excellent papers. In the accessible parts of the province they summarize conditions as follows: "Spring pollinosis is due to trees and shrubs. Of the trees, the most important are the poplars, elm, Manitoba maple and oak. Of the shrubs, the most outstanding are the willows, birches and alders. Their distribution and pollination characteristics are recorded. Summer pollinosis is caused by the grasses of which timothy, June grass and redtop are the most important. Their distribution and pollination habits have been described. Pollinosis in the autumn is due almost entirely to weeds. The weeds of greatest importance are the giant and perennial ragweeds, the burweed marsh elder, the Russian thistle, the burning bush and the sages. . . . The time and amount of pollination varies greatly from year to year."

New Brunswick, Nova Scotia, and Prince Edward Island*Field Studies:*

Provinces as a whole, 1940, H. Groh and W. H. Minshall.

In 1940 the only area of significant ragweed infestation was in the Annapolis Valley of Nova Scotia on the south shore of the Bay of Fundy, east to Minas Basin. No information on seasons or relative incidence of air-borne pollen is so far available.

Ontario*Field Studies:*

Province as a whole, 1937, H. Groh.

Province as a whole, 1940, H. Groh and W. H. Minshall.

Observations in Toronto and Niagara Falls and in southern edge of province from Windsor to Buffalo, by author (O.C.D.).

Atmospheric Records:

Cochrane, summer and fall, 1934, 1935, by author (O.C.D.).

Hamilton, 1942-1947, R. F. Hughes, M.D.

Kenora, 1940, C. H. A. Walton, M.D., and Margaret G. Dudley, Ph.D.

Ottawa, 1931-1933, by author (O.C.D.).

Parry Sound, 1934, 1935, by author (O.C.D.).

Port Arthur, 1931-1933, by author (O.C.D.).

Toronto, 1934, F. LaRush.

Toronto, summer and fall, 1930-1933, by author (O.C.D.).

Tree season, April and May.

Grass season, June and early July.

Ragweed season, August and September.

In the agricultural area of extreme southern Ontario ragweed conditions are the same as in adjacent areas of Michigan and New York State. The ragweed pollen index at Windsor, for example, is necessarily the same as for Detroit. The figure at Hamilton is the same. However, on the north side of Lake Ontario at Toronto the total amount of pollen in the air is less but still as high as at places of equivalent latitude in New England. Farther north in the province the amount diminishes rapidly. The chenopods seem not to be a factor and there is probably not enough biennial sage in the Great Lakes region to do any harm. The grass season is typical of the Great Lakes area with the same grasses noted for New York State and Michigan. Birch, ash, elm and oak are outstanding producers among the trees at Toronto. The reports by Detweiler and Hurst, also by LaRush, should be consulted.

Quebec*Field Studies:*

Province as a whole, 1937, H. Groh and W. H. Minshall.

Combined Field and Atmospheric Studies:

Gaspé Peninsula and southern Quebec, atmospheric tests in 21 cities and communities, see ragweed index, page 527, 1935-1945, Elzéar Campagna, Dr. Sc.

Atmospheric Records:

Father Point, summer and fall, 1934, 1935, by author (O.C.D.).

Montreal, summer and fall, 1930-1933, by author (O.C.D.).

Tree season, April and May.

Grass season, mid-May to early July.

Ragweed season, August and September.

The surveys of Groh and Minshall revealed a moderate infestation of short ragweed in that part of Quebec adjacent to New York and Vermont and a negligible amount east and north of the city of Quebec. These findings are confirmed by the more recent studies of Elzéar Campagna who has made a very thorough study of air-borne pollen, particularly in the Gaspé Peninsula. Campagna's figures are a bit difficult to standardize but by comparing his results at Montreal with my own, I have assigned indices (page 527) which are probably approximately correct. At least they are relative for the whole area. One striking feature is the great variation in pollen incidence in particular places from year to year. Sages, chenopods and plantain are probably not important but there is a possibility of some activity from plantain. No data are available regarding tree pollens.

Saskatchewan

Atmospheric Records:

Prince Albert, summer and fall, 1930, by author (O.C.D.).

No field studies have been reported. My tests at Prince Albert in 1930 revealed only a trace of ragweed pollen. Several years later Walton and Dudley found a small amount 150 miles east and a little north of Prince Albert and larger amounts in southern Manitoba. Russian thistle is undoubtedly more important than ragweed in the wheat raising districts. Poverty weed (*Iva axillaris*) is present but probably unimportant.

Mexico

Combined Field and Atmospheric Studies:

Mexico Valley (Mexico City and vicinity), 1940, M. Salazar Mallen, M.D., and P. Lyonnet.

Atmospheric Records:

Mexico City, summer and fall, 1932, 1933, by author (O.C.D.).

Tampico, summer and fall, 1932, by author (O.C.D.).

From ragweed records taken at Brownsville, Texas, on the Mexico border, it is evident that ragweed pollen is a hay fever factor in the adjacent corner of Mexico. However, the weeds must diminish considerably in amount southward to Tampico. There is very little ragweed at Mexico City. In the border states conditions must be judged by records at such points as El Paso, Imperial Valley and San Diego. Salazar Mallen considers the amaranths to be important in Mexico Valley. He mentions only *Amaranthus hybridus* and *A. retroflexus*, neither of which has ever been proved to be clinically active in the United States. Palmer's amaranth is known to be present in Mexico Valley and probably in the northwestern part of Mexico. Grass pollen is considered important in Mexico Valley. Salazar Mallen emphasizes Bermuda grass. This author lists the following trees as sources of the greatest amount of air-borne tree pollen in Mexico Valley: ash, cedar, alder, and oak.

Bermuda Islands

Field Studies:

Bermuda Islands, 1940, by author (O.C.D.).

Bermuda Islands, 1935, H. Hodgson.

Combined Field and Atmospheric Studies:

Bermuda Islands, 1941, Leslie N. Gay, M.D., H. Curtis, M.D., and T. Norris

Because of unfavorable soil and atmospheric conditions weeds and grasses are rare and very unlikely causes of allergy in the islands. Atmospheric tests by Gay and his associates revealed large quantities of cedar (*Juniperus bermudiana*) pollen in the air during the month of March. A few people suffer inhalant allergy symptoms because of this pollen. Thus Bermuda can be considered the most favorable island hay fever haven immediately available for citizens of the United States and Canada.

Cuba and Puerto Rico

Cadreeha Alvarez and Quintero Fossas have carried out field and atmospheric studies in these two countries where conditions are essentially the same. Little if any hay fever is caused by the pollen of tropical plants. The soil and climate are not conducive to the growth of weeds. Some ragweeds are present but atmospheric contamination is almost nothing. Bermuda grass is regarded as the most common source of grass pollen hay fever. Again the amount is very small. Sugar cane is a possible source of grass pollen in certain areas.

RAGWEED POLLEN INDEX

FOR THE UNITED STATES AND ADJACENT AREAS

(REVISED 1948)

The figures given are based on an arbitrary scale which includes three factors: length of season, intensity of occasional atmospheric concentration, and total seasonal catch on the test slides, as explained in my article on evaluation of hay fever resorts (1937). The figures in parenthesis are based on incomplete data, or are transferred across state lines from near-by points. Any area with a rating above 10 cannot be regarded as a suitable refuge for ragweed hay fever sufferers. Those rated below 1 are certainly to be preferred.

Alabama		Florida	
Birmingham	(33)	Coral Gables	2
Mobile	8	Jacksonville	1
Alaska		Miami	0.07
Fairbanks	0	Orlando	(1)
Juneau	0	Tampa	8
Nome	0	Georgia	
Arizona		Atlanta	36
Phoenix	1	St. Simons Island	77
Grand Canyon National Park		Idaho	
Grand Canyon	0.12	Boise	5
Arkansas		Moscow	(0.5)
Little Rock	47	Sun Valley	0.25
West Memphis	(76)	Illinois	
California		Bloomington	89
Alpine	3	Chicago	75
Arcata	3	Decatur	153
El Centro	1	East St. Louis	(114)
Escondido	1	Grayslake	63
Oakland	0.2	North Chicago	86
Lassen Volcanic National Park	0.032	Peoria	113
Los Angeles	1	Rockford	108
Pasadena	0.87	Rock Island	113
Sacramento	0.24	Springfield	74
San Diego	1	Streator	67
San Francisco	0.24	Indiana	
Sequoia National Park	0.03	Cicero	76
Yosemite National Park	0.29	East Chicago	(75)
Colorado		Indianapolis	100
Burlington	(23)	Jeffersonville	(102)
Colorado Springs	30	Iowa	
Denver	31	Ames	87
Estes Park	1	Council Bluffs	(94)
Rocky Mountain National Pa.		Des Moines	140
Grand Lake	0.18	Iowa City	83
Pikes Peak	0.9	Kansas	
Connecticut		Goodland	23
Bridgeport	37	Kansas City	(109)
New Haven	29	Wichita	73
Sherman	13	Kentucky	
Waterbury	24	Covington	(58)
Delaware		Louisville	102
Wilmington	(46)	Louisiana	
District of Columbia		New Orleans	43
Washington	45	Tallulah	(33)

Maine		Ludington	60
Augusta	9	Mackinaw City	13
Bar Harbor	8	Mackinac Island	19
Camden	9	Mancelona	39
Eastport	6	Manistee	54
Greenville	4	Manistique	12
Houlton	1	Marquette	12
Kineo	27	Menominee	37
Machias	4	Mt. Pleasant	74
Newagen	1	Munising	16
Poland Spring	12	Newberry	20
Portland	25	Northport	25
Presque Isle	1	Ontonagon	13
Rangeley	9	Petoskey	30
Rockland	8	Port Austin	107
Southport	8	Powers	21
Speckle Mt.	2	Rogers City	19
Upper Dam	2	Rosecommon	21
York	8	St. Ignace	8
Maryland		St. Joseph	103
Baltimore	49	Sault Ste. Marie	4
Takoma Park	645	Stambaugh	24
Massachusetts		Traverse City	39
Amherst	25	West Branch	31
Boston	17	Minnesota	
Nantucket	20	Duluth	44
Newton Center	14	Minneapolis	99
Northampton	20	Moorhead	125
Winchester	19	Rochester	67
Worcester	22	Tower	6
Michigan		Mississippi	
Alpena	20	Biloxi	7
Ann Arbor	122	Vicksburg	33
Bad Axe	40	Missouri	
Baldwin	41	Kansas City	109
Bay City	72	St. Louis	114
Benton Harbor	110	Montana	
Big Rapids	57	Glacier National Park	
Blaney	16	Belton	0.10
Boyer City	35	Many Glacier	0.07
Cadillac	31	Miles City	4
Charlevoix	21	West Yellowstone	0.16
Cheboygan	23	Nebraska	
Cold Water	190	Lincoln	63
Copper Harbor	5	North Platte	13
Crystal Falls	14	Omaha	94
Detroit	83	Scottsbluff	38
East Tawas	75	Nevada	
Escanaba	57	Reno	0.1
Flint	76	Lake Mead	4
Frankfort	65	Lake Mead National Recreational	
Gaylord	54	Area	4
Gladwin	99	New Hampshire	
Grand Haven	90	Bethlehem	5
Grand Rapids	126	New Jersey	
Grayling	52	Atlantic City	30
Grand Traverse	37	Maplewood	14
Harbor Bay	64	New Brunswick	8
Hillsdale	78	Pitman	54
Houghton	9	Teaneck	11
Ironwood	17	Verona	1
Isle Royale National Park	2	New Mexico	
Lake City	33	Albuquerque	1
Lansing	94	Roswell	1

New York		Pawhuska	31
Albany	36	Tulsa	65
Big Indian	23	Oregon	
Big Moose	7	Portland	0
Buffalo	75	Crater Lake National Park	0.072
Coney Island	23	Pennsylvania	
Croton	29	Altoona	52
Elsmere	49	Broomal	40
Fire Island	23	Hatboro	48
Garden City	22	Philadelphia	58
Haines Falls	5	Pittsburgh	59
Hague	16	Rhode Island	
Hewlett	(22)	Block Island	31
Indian Lake (Blue Mt. Lake)	1	Providence	21
Lake Placid	17	South Carolina	
Long Lake	3	Charleston	11
Loon Lake	7	South Dakota	
Lowville	20	Aberdeen	17
McKeever	5	Mobridge	10
Mineola	(30)	Pierre	14
New York, Metropolitan		Rapid City	18
Bronx	26	Sioux Falls	52
Brooklyn	20	Tennessee	
Manhattan	29	Great Smoky Mountains National Park	
Flushing	28	Headquarters	13
Jamaica	35	Newfound Gap	4
Rockaway	27	Knoxville	49
Staten Island	27	Memphis	76
Ozone Park	(28)	Nashville	60
North Creek	12	Texas	
Old Forge	0.15	Amarillo	1
Pine Hill	6	Brownsville	24
Plattsburg	36	Corpus Christi	30
Remsen	11	Dallas	120
Rochester	51	El Paso	1
Saranac Lake	5	Fort Worth	71
Speculator	9	Galveston	36
Syracuse	43	Houston	68
Tannersville	6	San Antonio	27
Tupper Lake	13	Utah	
Wanakena	8	Salt Lake City	3
White Plains	27	Zion National Park	0.33
Windham	29	Virginia	
North Carolina		Alexandria	(45)
Asheville	58	Charlottesville	35
Charlotte	43	Richmond	42
Great Smoky Mountains National		Washington	
Park, Newfound Gap	(4)	Seattle	0
Hatteras	71	Spokane	0.06
Raleigh	28	Mt. Rainier National Park	
North Dakota		Longmire	0
Fargo	(125)	Paradise Valley	0.12
Ohio		White River	0.036
Akron	100	Olympic National Park	(0.05)
Cincinnati	58	West Virginia	
Cleveland	74	White Sulphur Springs	19
Toledo	98	Wisconsin	
Youngstown	61	Eagle River	13
Oklahoma		Madison	125
Fort Sill	(73)	Milwaukee	108
Henryetta	(75)	Plum Island	40
Muskogee	85	Sheboygan	90
Oklahoma City	73	Superior	(44)
Okmulgee	57		

Wyoming		Charlesbourg	2
Lander	23	Farnham	64
Yellowstone National Park		Father Point	1
Mammoth	0.16	Gaspé	1
West Yellowstone (Montana)	0.16	Grande Rivière	0.02
		Iles-de-la-Madeleine	0.07
Canada.—		Lac-des-Seize-Iles	0.87
Manitoba		Lennoxville	4
Brandon	2	Matapédia	0.06
Dauphin	5	Mont-Albert Gaspésie	0.06
Morden	12	Mont Joli	0.21
Pierson	6	Montreal	30
Russell	1	New Carlisle	3
The Pas	0.05	Normandin	3
Winnipeg	8	Percé	0.17
Ontario		Quebec	3
Cochrane	2	Rimouski	0.57
Hamilton	64	Ste-Anne-de-la-Pocatière	0.91
Kenora	10	St-Lambert	5
Ottawa	11	Saskatchewan	
Parry Sound	8	Prince Albert	0.08
Port Arthur	7	Mexico.—	
Toronto	23	Mexico City	0.26
Windsor	(66)	Tampico	4
Quebec		Matamoros	(24)
Berthierville	33		
Carleton	0.17	Bermuda.—	
Chandler	14	Hamilton	0

CHAPTER XLIV

PLANTS WHICH CAUSE POLLINOSIS

THE GYMNOSPERMS

Pine. *Pinus L.*—The conifers comprise a long list of evergreens, the pines, spruces, hemlock, tamaracks, larches, firs, cypresses, arborvitaes, cedars, junipers and the sequoia or redwood. With one exception none of these has been shown to be responsible for hay fever, in spite of the fact that they shed tremendous amounts of wind-borne pollen. The allergist will not infrequently find pine pollen on the slide. Our interest in pine is therefore primarily for recognition of its distinctive pollen grains. (See Fig. 105.)

Air bladders are found in no other pollens of trees living today. Fossil tree pollens often contain them. This is further evidence that the gymnosperms, the conifers, are lower evolutionary forms than the angiosperms.

When moist, pine pollen is seen to consist of three general parts, the main body to each side of which is attached a wing, distended with a bubble of air, the air bladder. Connecting the wings the body of the grain is roughly rhomboidal with a long convex surface on one side and short convex surface on the other, bringing the two bladders much closer together on this side. It is in this shorter convex portion that the germinal furrow is located. The exine is thin and protects poorly here, but on the outer convex surface it is adequately thickened. With drying, the germinal furrow is drawn in. As a consequence, the two air bladders are brought close together, thus closing and protecting the germinal furrow. Thus, we see that a moist pine grain has its wings spread like a bird while the partially dried grain has them folded. The air bladders therefore appear to serve two functions, greater buoyancy and protection for the germinal furrow.

Rowe has found sensitization to tamarack pine and relieved symptoms through hypsensitization.*

Mountain cedar. *Juniperus sabinoides Nees.*—Most so-called cedar in the United States is in reality juniper. The only true cedars of importance are deodar and cedar of Lebanon which have been planted sparingly as ornamentals. So-called cedar of the South and Southwest is juniper. Mountain cedar or Mexican cedar is an important hay fever plant in central Texas, somewhat less so in eastern Texas, Arizona and New Mexico. It is not limited to the mountain ranges since it is also used in the cities as an ornamental tree.

Pollinating period is from about December 20 until early March. Since the plant is often used in the Southwest as a Christmas tree, it is at times responsible for pollinosis at Christmas time.

Red cedar, *Juniperus virginiana L.*, is quite common south of Virginia, Tennessee and Arkansas and may be responsible for sporadic cases. It flowers in March and April but sheds little pollen. I have observed positive skin reactions but have never found it necessary to treat for cedar pollinosis. Cedar is the predominant tree in Bermuda. I have seen one patient who gave positive skin reactions to cedar (juniper) and who regularly developed hay fever in a certain room in his Bermuda home which was paneled with cedar wood.

Cedar pollen is a small spheroidal grain which when dry appears somewhat crumpled.

Port Orford Cedar is native of Oregon and California. It has not been described as responsible for hay fever but Black finds that its pollen, closely related to that of mountain cedar, cross reacts by skin test and that the mountain cedar patient may be desensitized equally well with mountain cedar pollen or Port Orford pollen.

Cypress. *Taxodium distichum L.*—Although the writer has observed positive skin reactions, this appears not to be a pollen of importance. Bald cypress grows in moist areas, especially swampy sections from Delaware south along the coast and in the lower reaches of the Mississippi Valley. The tree is not plentiful but there are certain sections in which it is locally abundant and might cause pollinosis. It deserves further study locally.

The pollen is like that of juniper, although slightly larger. Pollination occurs in March and April.

(See Fig. 109.)

*Rowe, Albert H., Oakland, California. Personal communication.



Fig. 105.—Pollens. Pine in oil (upper left) is more translucent than in saline (upper right), and is shrunken, the air bladders being drawn together. Tamarack (below) illustrates the ease with which some pollens may break from application of pressure on the cover slips. All pollens photomicrographed in this series are proportionately enlarged, so that the indicated relative sizes are significant.



Fig. 106.—Mountain cedar in eastern Texas.



Fig. 107.—Mountain cedar. In Texas this is widely used as an ornamental and is not at all confined to the mountains. Right, detail of mountain cedar.

ANGIOSPERMS

The Monocotyledons

The gymnosperm with its unprotected seed is of lower evolutionary order than the angiosperm whose seed is enclosed in a case. In the latter group the lower or simpler form is the monocotyledon, possessing but one seed leaf or

storage leaf, exemplified by the grasses and cereal grains, while the higher form of angiosperm, the dicotyledon, has two seed leaves as exemplified by the two parts of a peanut, pecan, pea or bean. (See Fig. 73.)

Monocotyledons which are of more or less importance in pollinosis include cattail, date palm and the grass family.

Cattail. *Typha angustifolia* L.—As a cause of pollinosis this is unimportant. I have seen one farmer boy near whose home there was a marsh with much cattail, who had hay fever at the time of cattail pollination. He gave positive skin reactions and was promptly relieved by coseasonal cattail pollen hyposensitization. Cattail, therefore, may cause pollinosis in the occasional sporadic case.

The plant pollinates in June. Its point of greatest interest, like that of the pine, is in the character of the pollen grain.

We have seen that in the development of pollen grains the mother cell divides into tetrads and that the mature grains usually separate. With cattail, the tetrads persist and are found on pollen slides. All of the methods of tetrad combination described on page 449 may be seen in the cattail tetrad (Figs. 95, 111).



Fig. 108.—Cedar growing abundantly in the mountains near Santa Fe, said to be the chief local cause of tree pollinosis.

Cattail is wind pollinated, enormous quantities being shed.

Date palm. *Phoenix dactylifera* L.—This may cause endemic pollinosis. According to Prince, palm pollen is responsible for a very appreciable incidence of pollinosis in Galveston, where the tree is common as an ornamental. The grain is small, ellipsoidal, with a single deeply invaginated furrow extending on one side from pole to pole. When moistened the furrow evaginates to give an irregular globular form. When the grain is dried the lips of the furrow approximate, resulting in an effective protective closure.

The date palm is dioecious (living in two houses), that is, trees are male or female. Although it is insect pollinated (entomophilous) large quantities of pollen are shed, some of which is borne for some distance on the wind. In Galveston it pollinates through most of the year.

(See Figs. 110, 111.)

The Grasses

This comprises one of the largest plant families on earth. The composites are the largest (11,000 to 12,000 species) followed by the orchids (8,000) and the legumes (7,000). The grasses come next with 4,500 species, but in quantity



Fig. 109.—Pollens. Top left, hemlock (stained with methyl green); top right, cypress in oil; bottom left, arborvitae (methyl green); bottom right, cypress (in saline).

they probably take first place since about one-sixth of the entire vegetation of the globe is grass. Originally nearly half of the area of the United States consisted of prairies on which the chief plants were grasses. There are 1,100 species of grass in the United States. Even in as small an area as the state of Washington there are about 275 species.

The distribution of the natural grass sections of the United States, from the Pacific Coast to the Atlantic seaboard, is interesting. With reasonably abundant rainfall along the western coast there is proportionately abundant vegetation. Most of the moisture in the atmosphere has been precipitated by the time the mountain sections are reached by the prevailing winds. The region immediately east of the mountains is therefore arid. The flora of this desert region is necessarily made up of an entirely different type of plants from those of the Pacific Coast. Here there is little grass but an abundance of sagebrush. With increasing rainfall as we progress eastward one reaches the grass-covered



Fig. 110.—Date palm at Galveston responsible for endemic pollinosis. The pollinating period is long.

prairies. In the prairie section the soil is fertile and the rainfall fairly abundant but there are frequent prolonged dry spells. Through the East the prairies merge gradually into the region of the great deciduous forests which once covered the area east of the Mississippi. The transition is gradual, with no sharp lines of demarcation. In the East the grassy areas, much smaller than the broad prairie expanses and interspersed with tree-covered areas, are called meadows.

The chief types of extensive grass associations are exemplified by meadows, steppes and savannas. Meadows are moist grass lands. They are found in all zones. Steppes are dry grass lands lying in temperate zones. Examples are the Old World steppes of Russia, Hungary, Rumania and Spain, and the prairies of the western United States, also the pampas of South America. Savannas are dry tropical grass lands with a scattering of trees. Examples are the llanos of Venezuela and the patanas of Ceylon.

No adequate explanation has ever been given why trees are not naturally more abundant in the prairie sections. They grow well when planted by man and, along the streams, willows and cottonwoods are naturally abundant. The

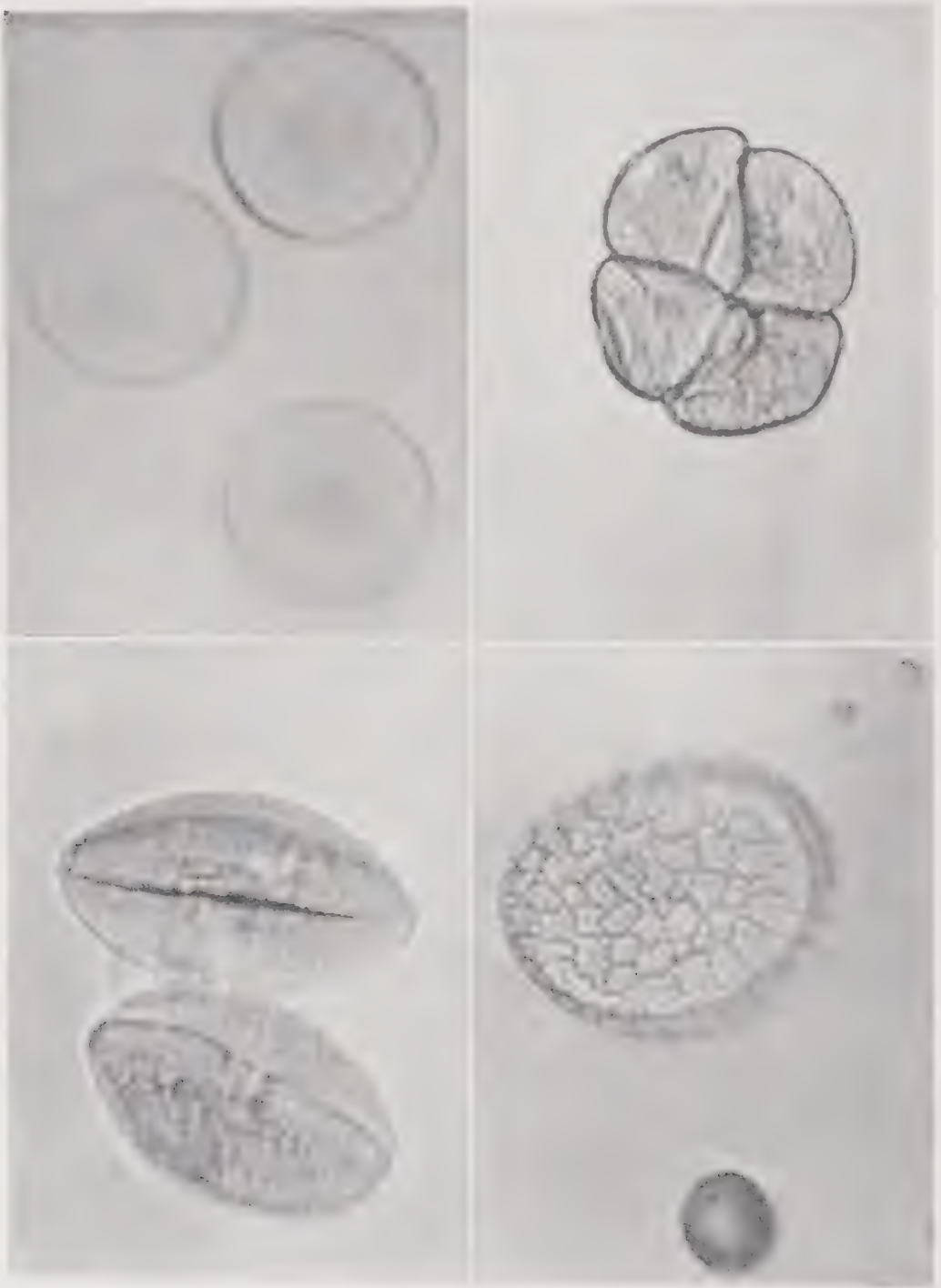


Fig. 111.—Pollens. Upper left, mountain cedar (methyl green); upper right, cattail (in oil); lower left, date palm (in oil); lower right, regal lily (in vaseline).

soil is appropriate for trees. It has been suggested that the Indians before the arrival of the white man burned the prairies regularly to keep trees out, so that there would be an abundance of grass for the buffalo herds. Grass recuperates after a fire much more rapidly than trees. It has also been suggested

that the buffalo themselves have eaten the small shoots of trees, thus preventing their growth. At any rate, once grass has gained a firm foothold, has established a good sod, it becomes very difficult for trees to get started. This is well illustrated in Texas with the mesquites. Prior to the advent of the Spaniard with his cattle, the arid Texas sections were good grass lands. Following destruction of the grass by stock, the mesquites have been able to grow as trees.

Factors influencing importance in pollinosis. Although there are 4,500 varieties of grass in the world, varying from the most insignificant to the majestic bamboo which may reach a height of 150 or even 170 feet, fortunately only a few are of major importance in pollinosis. The problem of hay fever grasses is simplified by several factors. First, there is a strong family interrelationship, crossed positive skin reactions being observed with most grass pollens and crossed desensitization being possible in the same manner as has been described above in the discussion of mountain cedar. For allergic therapy one need not necessarily know exactly which grass is furnishing the pollen. It usually suffices to know that some sort of grass is the allergenic excitant. Exceptions will be described later.

Another fact which materially simplifies the problem is that, although many varieties may be in a given locality, most are too sparse to create a sufficiently high atmospheric pollen concentration. For example, the grass hay fever season in New York is from the last week in May until about July twentieth. Thommen found about 270 different species of grasses within a hundred-mile radius of New York City. He found 8 blossoming in May, 34 in June, 41 in July, 41 in August and 15 in September. He tested 30 patients with 81 different species. All reacted positively to all species, while controls were negative. He even found positive reactions to a species of grass which grows only in Spain and to which the patients had not been exposed. Scheppegegrell had previously reached the same conclusion from the study of over 100 varieties of grass pollen. All reacted positively to all grasses although there was variation in the intensity of the reaction.

Although grasses in New York are pollinating into September the grass hay fever season ends earlier because of the limited delivery of pollen into the air in the later weeks. Most of the important hay fever grasses are cultivated grasses, growing abundantly in meadows and elsewhere where they have escaped and grown wild. This, we shall see, is especially true of Bermuda grass and Johnson grass in the South.

A third fact which helps to simplify the problem is that those very widely cultivated grasses from which we obtain our cereal grains, wheat, rye, barley, oat, rice and corn, fortunately produce very little pollen. Wheat, oat, barley and rice are self-pollinated. The major portion of the pollen remains in the flower, passing directly from the anther to the stigma. There is no wind pollination, not even insect pollination. The same is true of crab grass and probably of many other grasses which have been found unimportant hay fever causes.

Corn and rye are wind pollinated, but the former is of importance only when exposure is reasonably close. Corn pollen is one of the largest, averaging 95 microns in diameter, and is not carried far with the wind. (See Fig. 114.) However, I have seen a number of patients, farmers, who give positive reactions to corn pollen, stronger than those to the other grasses, whose symptoms are exaggerated during the corn pollen season. They are relieved with hyposensitization to corn extract. Rye is wind pollinated and would be a factor of more im-

portance in this country if rye were more widely cultivated. In Europe, especially in Germany where it is a very important crop, rye pollinosis is a problem of major importance.

The cereal grains are not known in the wild state. Their cultivation extends so far back into antiquity that even their places of origin are uncertain. Their wild counterparts have become extinct, or they have been so changed by cultivation that they are no longer recognizable, although wild plants have recently been discovered in Palestine which are believed by some to have been the progenitors of wheat.

All of the important hay fever grasses in this country were also originally imported, chiefly for cultivation for fodder.



Fig. 112.—Structure of grass blades. The blade originates at a node on the stem or culm and extends upward as a sheath closely wrapped about the culm. At the collar it leaves the culm to become the blade. Collar structure varies in different grasses and may be used for identification. Some are hairy, while others are not. The manner of its attachment around the culm varies as do the size and shape of the ligule (see Fig. 113). Since the collar structure including the ligule is constant in different species, its study is of value in identification prior to inflorescence. (Left, blade in place around culm. Right, blade removed from culm.)

The grain grasses were the first plants to be cultivated by the human race.

Anatomy. A number of characteristics differentiate the grasses from other plants. The stems are rounded, hollow and are jointed as in the familiar bamboo. In the smaller grasses the leaves take origin from the joints, thus concealing them in great measure. Only at the nodes or joints are the stems or culms solid. The strength of the stem is due in great measure to the quantity of silicon deposited therein.

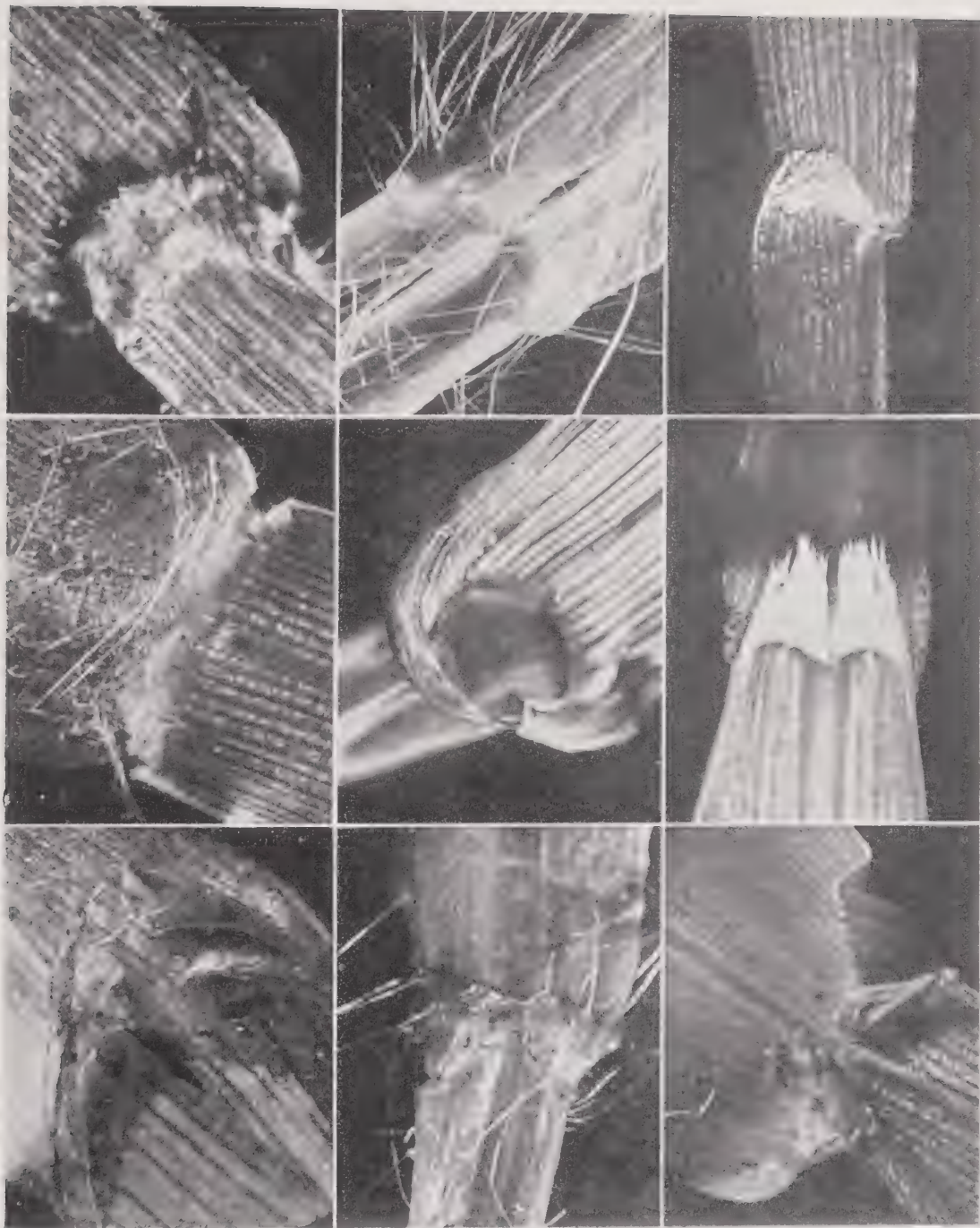


Fig. 113. — Collar structure of grasses. The collar may contain a small membranous tongue-like appendage, the ligule. The collar itself is a narrow band, more or less differentiated from the blade and sheaf. The margins of some collars are hairy, while others are glabrous or hairless. Auricles are earlike or clawlike appendages projecting from the edges of the collar to grasp the culm. They may be small, large, hairy or glabrous, or absent.

Top row: 1, Velvet grass. The collar is continuous, slightly hairy. There are no auricles. The ligule is short and membranous, coarsely toothed at the apex, and hairy on back. 2, Poa, sedge. The collar is small, hairy, in two parts, separated in the middle by broad wags. There are no auricles. The ligule is membranous, hairy on the back, and fringed with long hairs. 3, Redtop. The collar is narrow, divided into two parts by a space, glabrous, hairless. There are no auricles. The ligule is membranous, thin, very long, acute, finely toothed.

Middle row: 1, Foxtail. The collar is narrow, hairy, and the ligule is a fringe of hair, longest near the margins. There are no auricles. 2, Barley. The collar is broad, prominent, with one side higher than the other, and the auricles consist of large claws clasping the stem in spiral formation. The ligule is membranous, medium length, and the sheaves are sparsely hairy. 3, Johnson grass. The collar is broad. There are no auricles. The ligule is membranous, long, obtuse, mucronate ciliate at the top.

Bottom row: 1, Orchard grass. Collar broad, prominent. No auricles. Ligule thin, membranous, very long, often lacerate. 2, Crab grass. Collar broad, prominent, sparsely hairy. No auricles. Ligule membranous, long, acute, toothed. 3, Small crab grass. Collar broad, sparsely hairy. There are no auricles. The ligule is membranous, long, entire.

"The Key to the Identification of Grasses by Their Vegetative Characters" by LYMAN CARRIER, is available as Bulletin 161, United States Department of Agriculture. The descriptions are excerpted from this key.

A single leaf arises at each node, successive leaves being placed on opposite sides of the stem. The leaf as it passes upward from the node completely surrounds the culm at first, forming a tube. Higher up it spreads away from the culm as a long flattened blade. At the point where the leaf ceases to be a sheath and becomes a blade, there is a membranous or cartilaginous ring or fringe, the ligule. The ligule grasps the culm very much like a bracelet. It varies in size, shape and hairiness in different species and is useful in identification, Fig. 113.

The inflorescence or flower cluster consists of groups of flowers, each group being called a spikelet. Although the individual flowers of the grasses are so small as to be almost microscopic, they are beautiful when studied with adequate magnification. There are three general types of inflorescence, the spike, panicle and raceme. If the spikelets are attached directly to the main axis or rachis the inflorescence is a spike. Wheat, barley and rye are examples, Fig. 74. The Bermuda grass inflorescence is a raceme in which spikelets are borne on short branches of the rachis, Fig. 124. In the panicle there are several irregular secondary branches of the rachis, as is seen in June grass, red top and Johnson grass, Figs. 117, 122, 128. The timothy inflorescence is a panicle in which the branches are so crowded as to give the appearance of a spike, Fig. 120.

Roots.—The root systems are important. They explain the value of grasses in sod formation and the difficulty one encounters in trying to destroy some of those grasses which are not wanted. They possess no tap root as do radish, dandelion, beet, etc. Instead, the system is fibrous, composed of numerous slender roots of about equal diameter. Grasses may be annual or perennial. Those which are perennial grow up in successive years from horizontal underground stems or rootstocks known as rhizomes. Annual stems grow up from the perennial rhizomes. Rootstocks spread just beneath the ground, in all directions, often to surprising distances. From each node a stem may grow above ground. This underground system is valuable in the making of sod and is utilized in the planting of grass on dunes, to keep the sand from shifting. At the same time it makes it difficult to destroy such a grass in an undesired location, since even though the rhizomes be cut, new grass will grow from the cut sections and from this more rhizomes will be formed. This has been the great difficulty with Johnson grass which was imported into the South as a desirable crop grass but which, once established, can be removed only with greatest difficulty. Once escaped from cultivation, it has become a troublesome weed.

Rhizomes are underground stems rather than true roots, and, like the erect stem bear nodes, from which new erect stems take their origin. The interval between nodes is known as the internode. When the internodes of the rhizomes are short the vertical stems or culms are close together. The result is a tufted grass or bunch grass. Such a grass is often seen in fields and meadows but is not desirable as a lawn grass because of this characteristic. Lawn grass has long internodes in the rhizome. The culms are more widely separated. Such are called creeping grasses.

Stolons.—Some grasses have horizontal stems at or above the surface of the ground, known as runners, or stolons. This is comparable to the stolons of strawberries. Stolons are about as effective as the underground rhizomes in propagation. They usually have longer internodes, producing a more open or looser tuft. The sod is not as solid as that produced by rhizomes and the stolons may be injured by trampling or close grazing. However, stoloniferous



Fig. 114.—Pollens. Upper left, crab grass (in saline); upper right, wheat (in saline); bottom, corn (in oil).

Note variation in size of these grass pollens as well as those of previous figures. Note germinal pore in wheat.

grasses create the same problems as do the rhizome-bearing grasses. Bermuda grass, like Johnson grass, has become a problem in many sections of the South because it propagates by both stolons and rhizomes.

Identification. Although identification of the common hay fever grasses is relatively simple, once one has learned their characteristics, further attempts at differentiation are best left to a competent botanist. Indeed, differentiation is at times so difficult that botanists of fair ability may find it desirable to send specimens to the Department of Agriculture for accurate identification. The beginner might confuse grasses with the closely related sedge family, but the stems of the latter are solid, not hollow, and usually three angled rather than round.

Pollen.—Grass pollens are all much alike although varying somewhat in size, from that of corn (95 microns) down to Bermuda grass (26 microns). This fact cannot be safely used in identification except for corn. Specimen grains are spheroidal, ovoidal or ellipsoidal. Exine is thinned and entirely free from sculpturing. Intine is thick, hyalin. There is but one germinal pore. This is unique among pollens. There is no true germinal furrow, the shrinkage on drying being irregular, not along the line of a furrow, made possible because of the thinness of the exine. The germinal pore is covered by a small cap, the operculum. (See Fig. 114.)

CHAPTER XLV

THE HAY FEVER GRASSES

In accordance with Thommen's postulates pollen must (1) contain a hay fever excitant; (2) be anemophilous; (3) be produced in sufficient quantity; (4) be sufficiently buoyant to be carried long distances; and (5) the plant must be widely and abundantly distributed.

In the preceding chapter we have seen that the majority of grasses fail in one or more of these requisites. Some are not sufficiently abundant. Some are self-pollinated, producing too little pollen. Some pollens, like corn, are heavy and do not carry long distances. While all that have been tested appear to contain the allergic excitant, they do so in varying degrees.

On the basis of compliance with his postulates and of his experience with hay fever, Thommen classes the hay fever grasses as follows:

Grasses of Primary Importance

1. Timothy
2. June grass
3. Bermuda grass

Grasses of Secondary Importance

1. Orchard grass
2. Johnson grass
3. Couch grass
4. Sweet vernal grass

Grasses of Minor Importance

1. Low spear grass
2. Meadow fescue
3. Panic grass
4. Canary grass
5. Velvet grass

Of the 1,100 varieties of grasses in the United States, only 12 need be considered as of importance in endemic or epidemic hay fever. Furthermore, Thommen believes that the first three alone account for fully 90 per cent of grass pollinosis. Timothy and June grass (blue grass) are chief offenders throughout Canada and the northern two-thirds of the United States while Bermuda grass is the chief offender throughout the southern half.

Wodehouse considers five grasses responsible for the greater part of grass pollinosis in the northeastern states—sweet vernal, June grass, orchard grass, timothy and red top. Of these, sweet vernal grass pollinates at the beginning of the season, followed closely by June and orchard grasses, both of which flower in May and June and which are in turn followed by timothy and red top, which shed pollen late in June and through most of July. Other common grasses such as barnyard grass, crab grass, foxtail grass and the witch grasses pollinate later, but since the hay fever season terminates with red top and timothy, they need not be considered of significance.

In the South, Bermuda grass, originally imported as a forage grass, has escaped from cultivation and is the most important hay fever grass. Its pollen is light and it has the longest flowering period of all the grasses. In the northern sections of the South its pollinating period is similar to that of June grass but in the Southwest it flowers from April to September and in some sections, as

southern Texas and southern California, practically throughout the year. Johnson grass, likewise an escaped grass, sheds much less pollen. The grains are large and heavy. Its importance is secondary to that of Bermuda.

Velvet grass is of chief importance in Washington, Oregon and northern California, west of the mountain ranges. According to Hall, there are about 25 species of grasses in California which are of some importance in pollinosis.

Grasses of Importance Especially in the North Arranged According to Date of Pollination

Low spear grass. *Poa annua* L.—Also known as annual blue grass, dwarf meadow grass and, in the West, walk grass, this is of minor importance in the East but, according to Rowe, more important in northern California. It is found scattered in meadows and waste places practically throughout the United States. The leaves are slender, yellowish green. The plants do not stand erect, but tend to sprawl flat on the ground. In some places it is used



Fig. 115.—Sweet vernal grass.

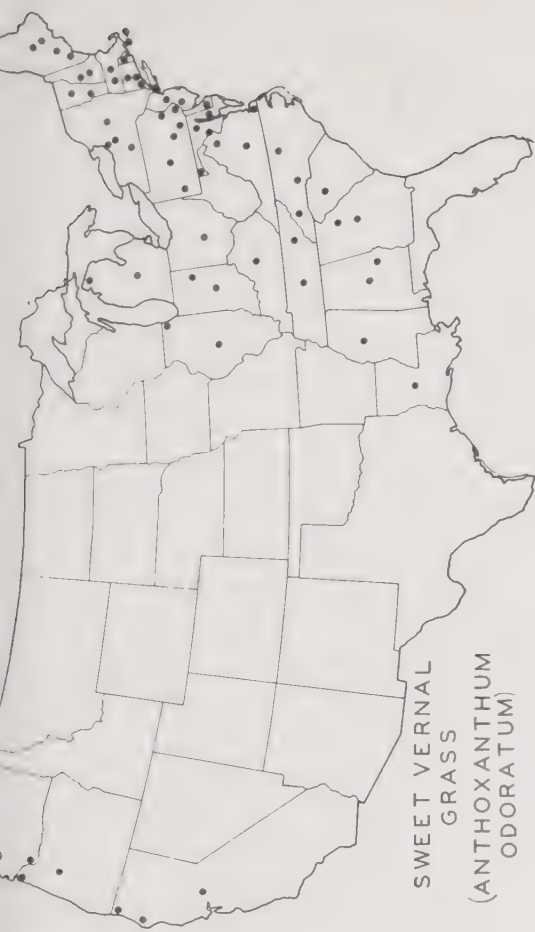
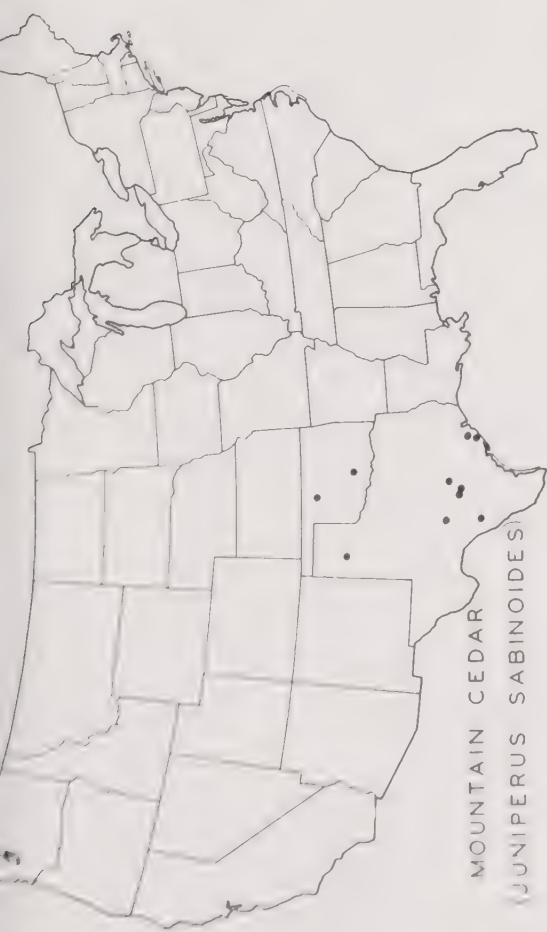


Fig. 116.

Figures 116, 125, 126, 168, 172, 181, 191, 211, 214, and 218.—Distribution of various hay fever plants as indicated by specimens obtained from localities represented by dots, and recorded in the National Herbarium in Washington. Shaded areas on certain maps are based on Durham's charts. The writer expresses appreciation to Mr. William H. Pease, for their preparation.

as a lawn grass, chiefly because of this last characteristic, but it dies out rather early in the summer. According to Wodehouse, pollination starts in the northeastern states in April. Thommen gives the date as the first week in June.

Sweet vernal grass. *Anthoxanthum odoratum* L.—Also known as prim grass and spring grass. This is not the same as *Hierochloë*, the sweet grass from which Indians of the northern states made sweet grass baskets and which is native of North America. Both owe their sweetish vanilla odor to the fact that they contain coumarin, also a constituent of vanilla. It is widely but sparsely scattered through the northern half of the country. According to Durham, it is of allergenic importance especially in New England. The writer finds it of importance also in the higher altitude of the Shenandoah Valley of Virginia. See Figs. 119, 120, 127.



Fig. 117.—June grass.

June grass. *Poa pratensis* L.—This is also known as Kentucky blue grass, common meadow grass, natural grass, green grass. It is undoubtedly the leading pasture grass in America. It is rarely cut for hay since it seldom grows large enough.

It owes its popularity as a stock grass to the fact that it is the most nutritious of grasses and is best liked by stock. In this country stock raising has never been a permanent feature of farming outside blue grass regions, except in the range country of the West where ranching takes the place of farming.

The distribution of blue grass is about the same as that of timothy. While it is found in all parts of the country, it is cultivated chiefly in the northeastern states as far south

as the Carolinas and as far west as eastern Kansas. It is the favorite lawn grass in this same section. Its name in the horse raising section of Kentucky is familiar to all. Its value as a lawn grass is due in part to the existence of rhizomes which form a good sod.

Although June grass is rarely allowed to flower on lawns, when fully developed in pastures and along the roadsides it stands about two feet high, as contrasted with its cousin *Poa annua* or low spear grass (see above) which never reaches a height of more than a few inches.

Pollination occurs in late May and early June.

See Figs. 116, 118, 119, 123.



Fig. 118.—Orchard grass.

Orchard grass. *Dactylis glomerata* L.—This is also called cock's foot, dew grass, hard grass. It owes its common name to the fact that it grows well in shaded places, under trees as in orchards. The English term, cock's foot, is derived from the remote resemblance of the inflorescence, in its branching, to a cock's foot.

This grass occupies the timothy and June grass region and, like red top, extends considerably farther south. It is adapted to drier soils than red top. As a hay grass it is of importance only in those sections where timothy does not grow. This is especially true in the

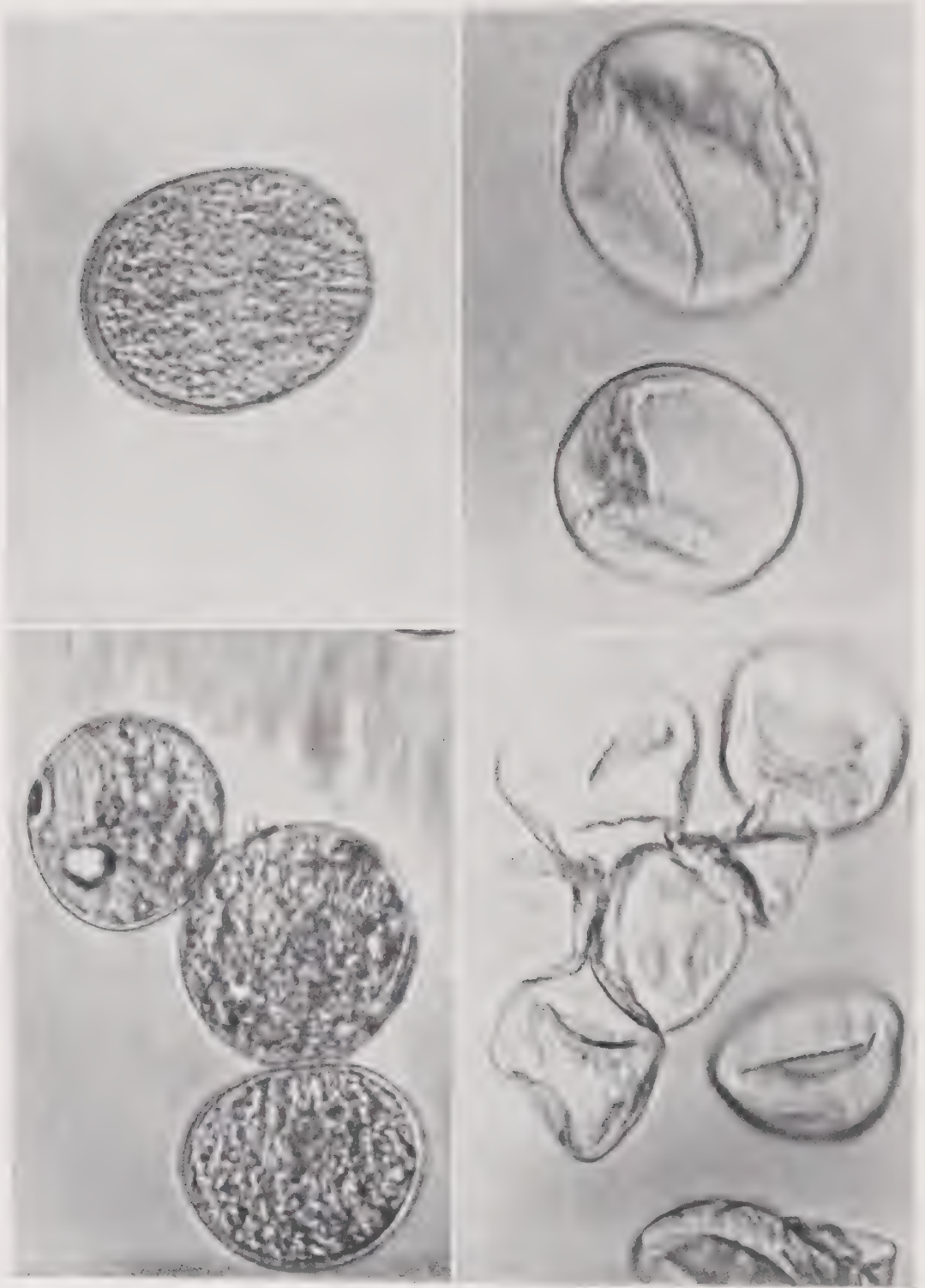


Fig. 119.—Pollens. Upper left, orchard grass (in saline); upper right, orchard grass (in oil); lower left, June grass (in saline); lower right, June grass (in oil).



Fig. 120.—Timothy.

soils along the base of the Appalachian Range from Virginia southward. In sections, where either may be grown for hay, timothy is preferred. Orchard grass tends to grow in bunches, making mowing difficult. If allowed to stand beyond the blooming period, it deteriorates as hay, due to the formation of woody tissue in the stem.

Its importance as a hay fever plant is secondary to that of timothy, merely because the latter is more widely cultivated. Skin test reactions to orchard grass are usually as large as, or larger than, those to timothy. Wodehouse considers it as important in pollinosis as timothy, possibly more so.

Pollination occurs in June.

Timothy. *Phleum pratense* L.—This is also known as Herd's grass, meadow cattail, rattail, soldier's feather. It is the most important hay grass in the United States, its acreage being twice as great as that of all other grasses combined. Although its hay is not as nutritious as that of June grass, it is readily eaten by all kinds of stock. It has excellent seed habits, the seed from an acre seeding a larger acreage than that from any other grass. It is considered especially valuable as hay for horses because of its favorable physiological effect on the digestive apparatus.

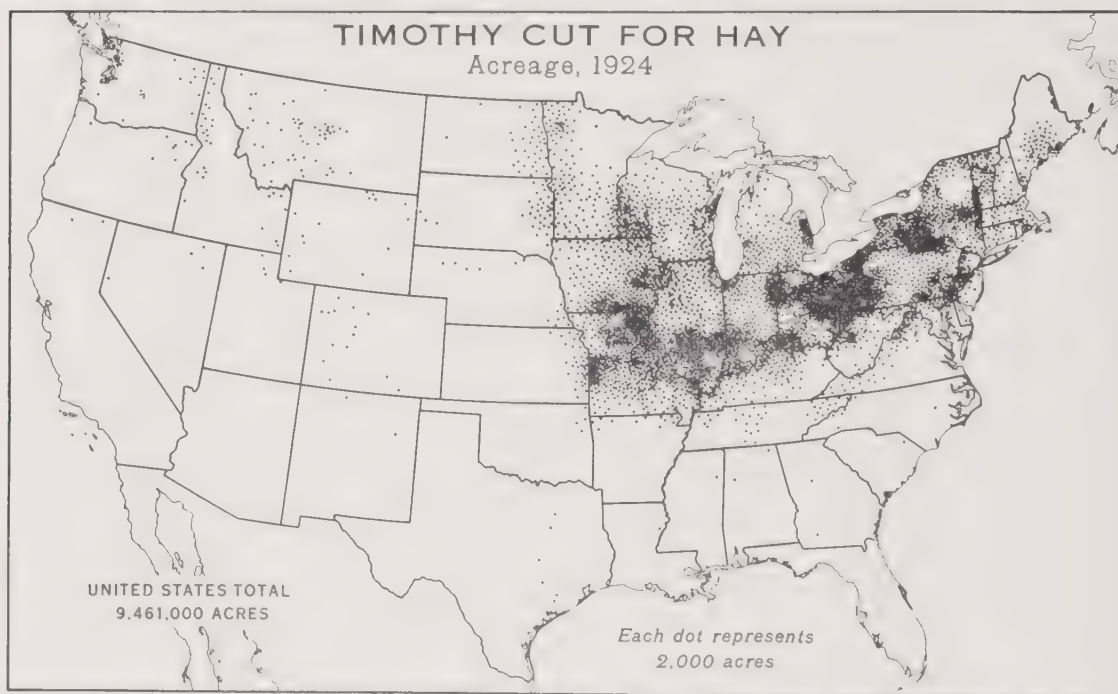


Fig. 121.—Distribution of cultivated timothy. In the Northern States, more abundantly toward the east. The escaped grass is also important. (Courtesy of Bureau of Agricultural Economics, United States Department of Agriculture.)

The grass derives two of its names from men, who either first cultivated it or first described it, about 1747. Herd was a New England farmer. Timothy Hansen lived in Maryland. The term timothy is now universal.

Timothy grows wild nearly throughout North America. It is cultivated over the same areas as blue grass—Canada and the northern two-thirds of the United States, but particularly in the northeastern states as far west as Kansas and Nebraska, and in restricted localities in the Rocky Mountains and Pacific Coast States.

The grass pollinates in late June and early July. The shedding of pollen occurs in the early hours of the morning, from shortly after midnight to shortly after sunrise.

See Figs. 120, 121, 123.

Redtop. *Agrostis alba* L.—It is otherwise known as Fiorin, Hehr's grass, white top, white, marsh or creeping bent, black quitch, tussocks, water twitch, fine John, monkey's grass, Burden's, summer dew grass, conch grass, bonnet grass.

This grass is cultivated in the timothy and blue grass regions and, like orchard grass, considerably farther south. Only in southeastern Illinois and adjacent parts of Kentucky



Fig. 122.—Redtop.

is it grown in preference to other grasses. In contrast to orchard grass which is adapted to dry soil, red top is a wet land grass and a valuable grass for moist meadows and pastures in all parts of the country except the extreme South. It is well adapted to the acid soils of the Atlantic seaboard. Its yield is inferior to that of timothy, but it withstands cropping and stamping by stock, better. It is nutritious but not as much so as timothy and June grass.

Although June grass and red top resemble each other much in appearance, they are rarely found together because June grass does not thrive in acid soil.

Pollination, like that of timothy, occurs in late June and most of July.

See Figs. 122, 123, 125.

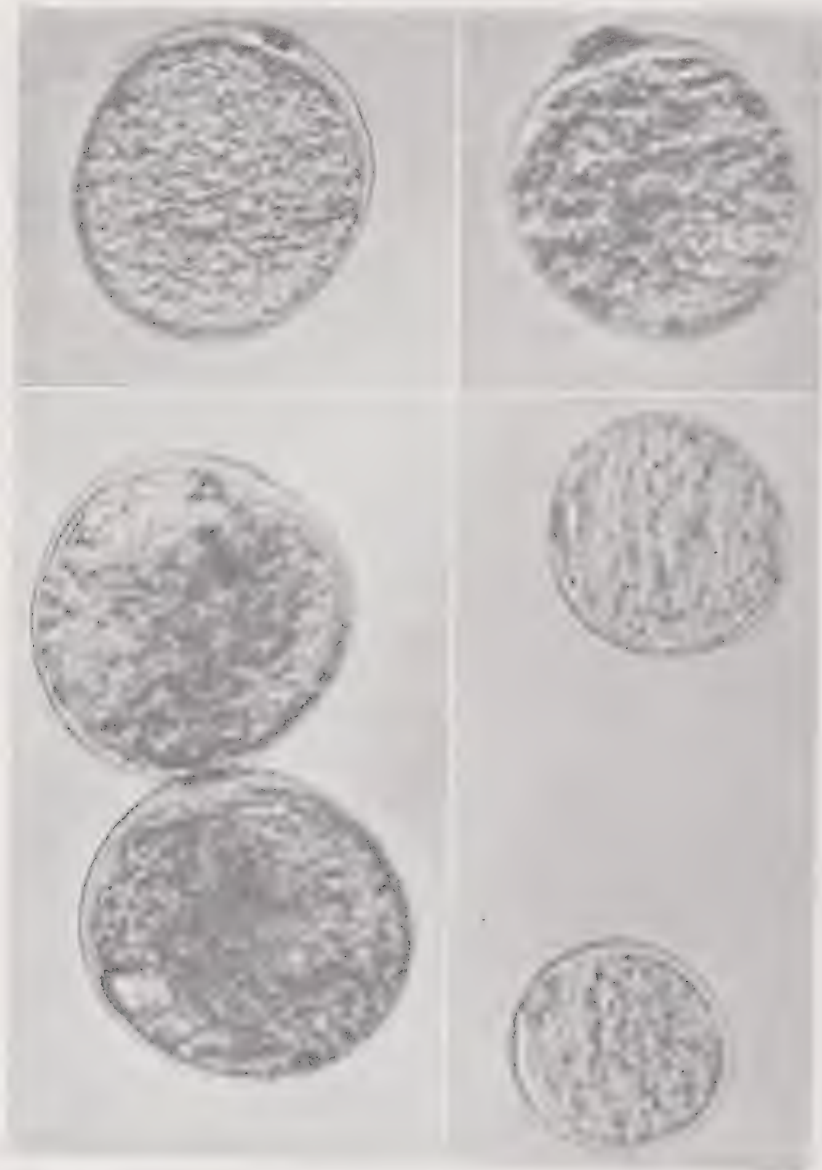


Fig. 123.—Pollens. Upper left, sweet vernal grass (in saline); upper right, Johnson grass (in saline); lower left, timothy (in saline); lower right, redtop (in saline).
Note single germinal pores on two top figures with operculum covering pore on Johnson

Grasses of Importance in the South

There is an overlapping zone of the important northern and southern grasses which includes and extends westward from Virginia and North Carolina. Sweet vernal, orchard and June grass, timothy and red top, as well as Bermuda

and Johnson grass, are all found in sections of Virginia. As stated above, orchard grass and red top extend farther south than the other northern grasses, but not into identical areas because of differing soil adaptation.

Bermuda grass. *Cynodon dactylon* (L.) Pers.—This is also called Scotch grass, dog's tooth grass, wire grass, cane grass, Bahama grass, Indian Doob. Although Bermuda grass may be found as far north as New York and Massachusetts, it is preeminently a grass of the South. Bermuda is to the South what June grass is to the North. It tolerates the heat of summer while blue grass grows very little in hot dry weather. It stands drought better. It furnishes good hay on good land, better even than June grass. It stands trampling better and yields more pasture. On the other hand, it furnishes pasture only during hot weather. Since the seed is unreliable and costly it is customary to start a stand by planting small pieces of sod from which stolons and rhizomes spread out to cover the neighboring ground. In times of drought the grass withers to the ground but with return of moisture it again springs up and bursts into flower.



Fig. 124.—Bermuda grass.

It is a native of Bengal
— Figs. 124, 125, 126.

Johnson grass. *Sorghum halepense* (L.) Pers.—Other names are evergreen millet, maiden-cane, Egyptian millet, cuba grass, Syrian grass, St. Mary's grass, Means grass.

This is a recent importation into the United States from Aleppo, Turkey. It was introduced into South Carolina about the middle of the last century where it was popularized by Governor Means. Later it was taken to Alabama by Colonel Wm. Johnson, whose name has since been applied. Although at first sown intentionally as a forage grass, it has become such a weed pest that chief interest now is in getting rid of it. It is a perennial, propagated by means of rhizomes. I have discussed the difficulty of removing plants which spread by this method. It is now widely distributed over the South from Virginia to Texas.



Fig. 125 See legend on page 515.



Fig. 12. — Pollens. Upper left, Bermuda grass (in saline); upper right, Bermuda grass (in oil); lower left, velvet grass (in saline); lower right, velvet grass (in oil).

and is found in California. Its distribution is very much the same as that of cotton. It is an important hay fever plant throughout the South but especially so in Texas, southern Arizona, and Oklahoma.

The grass grows to a height of from three to five feet somewhat resembling sugar cane or sorghum in appearance. The pollen is rather heavy and does not carry far. It is shed in relatively small amounts, but the wide distribution of the plant makes up for these deficiencies. Like Bermuda grass it is drought resistant. This is another reason for the difficulty in its eradication.

Pollination occurs during July, August and September.

See Figs. 123, 125, 127, 128.

Canary grass. *Phalaris canariensis* L.—“Bird seed grass,” an importation from the western Mediterranean section, grows in fields and waste places of the southern states, fairly abundantly in California, less so in the North. It blooms in July and August, but owing to its very meager distribution and the relatively large size of the pollens (40 to 45 microns) it is a decidedly minor factor in hay fever. See Fig. 125.



Fig. 127.—Johnson grass, growing to a height of three or four feet.

Additional Important Grasses in the West

Velvet grass. *Holcus lanatus* L.—Other popular names are meadow grass, wooly soft-grass, velvet mesquite, old white top, Salem grass, rot grass, dart grass, feather grass, whites, Yorkshire-fog, white timothy, calf-kill. This grass is common along the Pacific Coast. It is a profitable hay and pasture grass on sandy soil and on peaty soils that dry out in the summer. Stock do not like it but it is exceedingly nutritious, if not palatable, and they will acquire a taste for it when driven to it by hunger. It is found in the northeastern states but not in sufficient quantity to be of significance. Velvet grass is the most important hay fever excitant in the coastal regions of Washington and Oregon, less so to the north and south, in British Columbia and California, and is of no importance in the same two states, east of the Cascade Range. The blooming period along the Pacific Coast is from June to September.

The popular name is derived from the hairiness of the entire plant, especially the leaves. See Figs. 126, 129, 133.

Rye grass. *Lolium perenne* L.—This is also called ray grass, red ray, ever-grass, erap perennial rye, red Darnel, red dare, white nonesuch, English blue-grass.

See Fig. 130.

Italian rye grass. *Lolium multiflorum* Lam.—These two grasses are of some importance along the Pacific Coast. The Italian rye is the most important meadow grass in Europe.



Fig. 128.—Johnson grass, detail.



Fig. 129 Velvet grass.



Fig. 130.—Perennial rye grass.



Fig. 131.—Crab grass.



Fig. 132.—Paspalum.

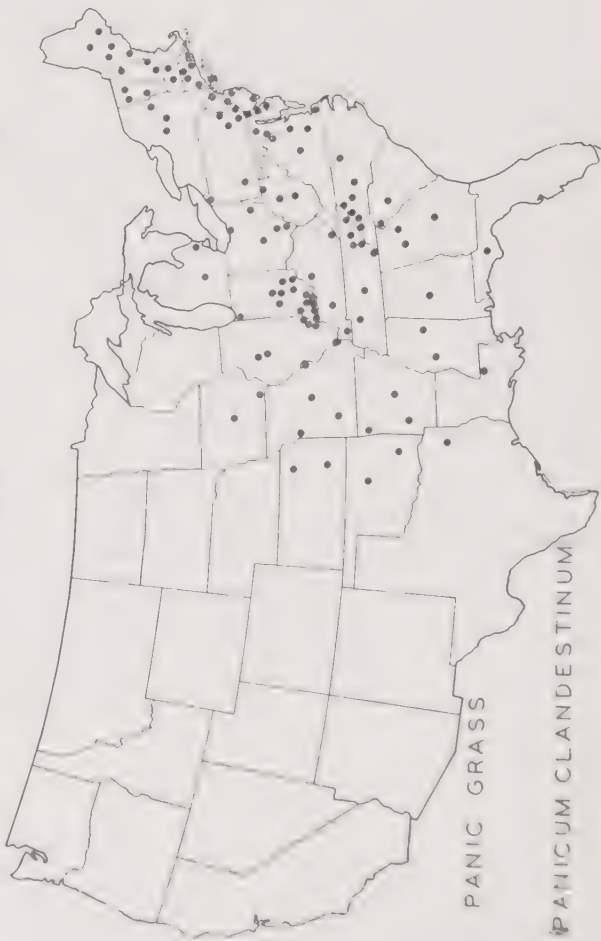


Fig. 133. See legend on page 132.

where it is relished better by stock than any of the other cultivated grasses. Both English rye and Italian rye are grown fairly abundantly along the Pacific Coast and to a slight extent as a late summer lawn grass elsewhere. On the coast, these grasses are of minor allergenic importance. Pollination starts in May and June.

Other Grasses of Very Minor Importance

Couch grass. *Agropyron repens* (L.) Beauv.—Also called quitch grass, quack grass, and by several other common names. Although in fields and waste spaces throughout North America, couch grass is particularly characteristic of the northern Rocky Mountain states where several species are valuable for forage. One variety is the common bunch grass of eastern Washington and Oregon and northern Idaho. It is a valuable range grass. *Agropyron repens* is the familiar quack grass of the northern states. It propagates by rhizomes and root stocks, and is a pernicious weed. It is valuable as a sand binder. Pollination occurs in June.

See Figs. 131, 133.



Fig. 134.—Foxtail, two varieties.

The Fescues, tall fescue and meadow fescue. *Festuca elatior* L. and *Festuca pratensis*.—According to Hitchcock (1935) these two grasses are the same. Next to the Italian and English rye grasses the tall and meadow fescues are the most important cultivated grasses in Europe. However, like the former, they have never been recognized as valuable in this country except in restricted localities such as western Missouri and eastern Kansas. Pollination is in June. *Festuca ovina* L., or sheep fescue, is one of the most abundant and valuable range grasses in the western mountain region.

Panic grasses.—These are several varieties, of which *Panicum clandestinum* L. appears to be the most important from the pollinosis standpoint. The panic grasses are widely distributed east of the Mississippi, especially in the southern states. They include crab grass, Colorado grass, Japanese millet and broome corn millet. Pollination occurs in June.

Paspalum. Like the panic group this is a large and important genus. The flowering grass resembles crab grass in appearance. Carpet grass which grows abundantly near the gulf coast will even drive out Bermuda when closely pastured. Knot grass (*Paspalum distichum* L.) is common in the South and frequently mistaken for Bermuda grass, which it resembles. Other common names are Dallas grass, tall paspalum, roadside grass, St. Augustine grass, flat crab grass, flat joint grass, Whittier grass. See Figs. 132, 133.

Spanish Moss.—*Dendropogon usneoides*

Spanish Moss.—*Dendropogon usneoides*, also known as Spanish moss, Hanging moss, Black moss, Florida moss, Long moss and Tree-beard, is a member of the pineapple family, *Bromeliaceae*. Botanically this monocotyledonous family belongs between the grass and lily



Fig. 135.—Spanish moss at Charleston, S. C.

families. The word dendropogon is derived from the Greek, meaning tree-beard. This is the gray moss which hangs from various trees, especially the live oak, and may be found throughout the southeastern states, south of Virginia, and west to Texas and Mexico. It is widely distributed in tropical America. Feder has found patients allergic to Spanish moss. Treatment was not satisfactory.* Metzger reports that the pollen is present in small quantities in the air near Tampa. With extracts of this pollen he observed two positive skin reactions among 30 persons who had symptoms during the period of pollination. He considered Spanish moss a factor of no great importance. The moss is used in the South as a filling for cheap pillows.

*Feder, J. M., Anderson, S. C.: Personal communication.

CHAPTER XLVI

ANGIOSPERMS

THE DICOTYLEDONS

In this chapter the order of listing follows that of botanical classification, rather than seasonal prevalence.

The Walnut Family. *Juglandaceae*

Black walnut. *Juglans nigra* L.—That walnut is not a more important hay fever plant is probably due to its relative scarcity. The writer finds positive skin reactions to walnut pollen as often as to that of elm. These trees were once abundantly distributed through the country, but because of the excellent wood most have been destroyed. English walnut is grown widely in California for its nuts. As a rule, this variety is grafted upon the black walnut trunk. See Figs. 136, 140.

English walnut, *Juglans regia* L., originated, not in England, but in Persia, along with apricot and peach. Its botanical name *Juglans* is derived from the Latin, meaning Jove's acorn. The Romans spoke of the walnut, rather than the fruit of the oak, as an acorn.

The pollen is very simple with no sculpturing. A varying number of pores replace the usual germinal furrows. Pores are usually more numerous on one hemisphere than the other. The exine is thickened on this side so that with drying the pollen usually shows an invagination of the thinner hemisphere.

Walnut pollen cannot be very toxic since it is often seen on pollen slides and patients frequently give positive reactions, but treatment is not usually necessary.

Pollination is usually in May and June.

Hickory. *Hicoria* Spp.—Hickory is a cousin of walnut. The leaf arrangement is rather different. The black walnut leaf is compound, about two feet long, with a dozen or more leaves, set opposite in pairs and with an odd one on the tip. The tip leaflet usually forms earlier than the others. The typical hickory leaf usually has but five, seven or nine leaflets. One is terminal. The pairs of lateral leaflets increase in size towards the tip.

The male flowers of both walnut and hickory are catkins.

The name hickory is derived from the milky oily liquor obtained by the Indians from pounding the kernels. It is strictly an American tree, there being nine species. It is distributed in varying prevalence from the valley of the St. Lawrence to the mountains of Mexico.

Shagbark hickory, *Carya ovata* (Mill) K. Koch, can be readily identified in the winter, prior to pollination, by its bark, which appears to be very loosely attached to the body of the tree in narrow vertical plates, free at both ends. Young hickory has a smooth bark but, as it grows, the trunk becomes furrowed and the bark splintered. This occurs only in trees six inches or more in diameter. By the time the tree bears nuts a real problem is encountered by those who attempt to obtain them.

Some trees pollinate before putting out leaves while others do so at that time or later. Both hickory and walnut pollinate after the leaves are about half grown. Even so, foliage appears rather late. As a consequence, pollen appears on the slide very late in the tree season, as late as May and June. See Figs. 136, 137.

The hickory pollen grain is larger and less flattened than that of walnut. There are usually only three germinal pores, rather equally spaced. Distinction from walnut lies in the fewer pores and the larger size.

Pecan. *Carya pecan* (Marsh.) C. K. Schneid.—This is likewise a native American tree, occurring in moist soil, especially along streams, in southern Indiana, Illinois, Iowa and southward to the Gulf. It is found along river bottoms in Texas. It is an important cause of pollinosis in the South, as far north as North Carolina. It is frequently planted as a shade tree in farm yards and, being near houses, produces a heavy local concentration of pollen.

Like the other two members of the family the leaves are feathery, with a number of leaflets. Like hickory, the leaflets near the base are smaller. Unlike it, so also are those at the tip. Pecan bears catkins. It pollinates from mid-April until early June.

The pollen resembles that of the other two members, is about the same size as that of hickory, usually has three germinal pores, and is more granular in appearance than the others. See Figs. 138, 139.

Weil has described an unusual case of a pecan pollen allergic. There was a pecan tree outside the bedroom window. While dressing, the patient laid her handkerchief on the window ledge. Subsequently she used the handkerchief. This was followed by an extremely severe attack.



Fig. 136.—Walnut. Leaves appear late and are shed early. The difference in this respect between the tree and surrounding foliage is apparent.

The Willow Family. *Salicaceae*

The botanical name for this family, which includes willows and poplars, is readily understood when we realize that salicylic acid is abundant in the bark of the willow. Tannic acid is abundant in poplar bark.

These two genera, especially poplar, are probably the earliest angiosperm trees. Poplar is the oldest dicotyledonous plant yet identified. When Greenland was covered with forests of pines, sequoias and cycads, poplar was the only deciduous tree on that warm continent. Both poplar and willow are widely distributed today. The former ranges from the Hudson Bay to Mexico, growing

farther north even than spruce and larch. One variety, cottonwood, is an important hay fever plant in the West, especially the Rocky Mountain section.

Willow. *Salix Spp.*—Willow grows nearer the North Pole than any other woody plant except birch. It enters the tropics, crosses the equator, and is found in the mountains of Peru and Chili. Its range in the Old World is as great. There are 160 species which hybridize among each other so widely that they are the despair of botanists. For this reason a great botanist once called the willows the "troublesome family." Like poplars the willows come from an ancient line. Fossil impressions of the leaves having been found in cretaceous rocks. Fossilized willow pollen is found in the peat of the Dismal Swamp of Virginia although living trees have long been absent or nearly so, from this region.



Fig. 137.—Pollens. Top, magnolia (boat-shaped, stained with methyl green); lower left, hickory (in saline); lower right, hickory (in oil).

In view of willow hybridization it is not surprising that allergenic specificity within the family has not been described. Willows are not of great importance in allergy. The pollen is both insect and wind transmitted. It is therefore often found on pollen slides, but is not of as much importance in hay fever as many of the purely anemophilous plants. Wodehouse believes that willow, having been unsuccessful in its trial of entomophily or insect pollination, is now evolving toward anemophily. Others believe that the reverse is occurring. Characteristics of the pollen as pointed out by Wodehouse favor the former conclusion. He believes it likely that willows and poplars are derived from a willow-like ancestor which was entomophilous, that poplars have become entirely wind pollinated, while willows are now evolving in the same direction.

Willows grow abundantly along the banks of streams where the well-developed root system protects the land against the erosive action of water.

They pollinate, depending upon species, anywhere from March to July inclusive, the majority in March, April and May. In most species flowering precedes leaf development. In some they occur simultaneously. Some pollinate after unfolding of the leaves. The first group is exemplified by the pussy willow whose gray furry catkin or ament, on the brownish stem without leaves, gives rise to its popular name. In some localities where there are several species, the pollinating period may extend over several months.

Willow pollen possesses three germinal furrows and a heavy reticulated exine. See Fig. 140.

The willow flower has a sweet scent and contains nectar, attracting bees and other insects.



Fig. 138.—Pecan in Texas. The native Texan has two rules for recognition of pecan. If a tree is left standing in a cultivated field it is probably pecan. If on closer inspection the nut husks can be seen, even in the absence of leaves, it is a pecan.

Aspen. *Populus Tremuloides* Michx.—This member of the poplar genus is the most widely distributed tree of North America. It prefers moist, sandy soil and gravelly hillsides. The botanical name *Populus tremuloides* and the popular designation, quaking asp, are derived from a peculiarity of the leaf, which is characteristic in some degree of all members of the poplar family. The petiole or leaf stem is unusually long, slender and compressed laterally, the compression being vertical to the plane of the leaf. As a consequence the leaf has an independent motion in a breeze quite different from that of other leaves more firmly attached to the branches. In the slightest breeze, too little to move a branch, the leaf quivers and trembles. Like most members of the poplar family the leaf is broad, almost circular, slightly heart shaped. The plant is distributed from the Hudson Bay region to Mexico. It is most abundant from Ontario to Virginia.

Pollination occurs from March into May.

The pollen of this and other members of the poplar family is smooth, with no surface markings, no germinal furrows or pores. The exine is extremely thin, thus allowing for change of volume with desiccation. It is reticulated or granular in appearance. Intine is thick. The thinness of the exine allows the pollen tubes to perforate in the absence of germinal pores. See Fig. 143.

Lombardy poplar. *Populus nigra* L. var. *Italica* DuRoi.—Although imported as an ornamental from the Italian province of Lombardy, this tree was unknown to the Romans

of the time of Pliny and appears to have originated in Afghanistan. It is the only deciduous tree whose branches hug the stem, a fact which makes it desirable for fences, hedges and where for some reason much shade is not desired. General characteristics of the leaf and pollen are similar to those of aspen.

Pollination occurs about April and May.

Cottonwood. *Populus deltoides* Marsh.—The scientific name *Populus deltoides* is derived from the delta shape of the leaf. As a rule this designation is applied to the Carolina cottonwood of the East, which is rarely a cause of hay fever. The western cottonwood, *Populus sargentii* Dode, is a most important cause of pollinosis in the Rocky Mountain section, from Utah and the Dakotas to New Mexico and Arizona, where it pollinates around March and April. In the West it grows chiefly along stream beds where there is sufficient moisture. The trees pollinate before the leaves are unfolded. See Figs. 141, 142, 143.

The cottonwood name is derived from the "cotton" or tomentum, the matted hairy covering of the seeds.



FIG. 139.

Figs. 139, 145, 146, 148, 149, 154, 160, 164, 185 and 196.—Show the distribution of forest trees of importance in pollinosis. (Courtesy of E. N. Munns, Chief of the Division of Forest Influences, Forest Service U. S. Dept. of Agriculture, Excerpted from U. S. Dept. of Agriculture Miscellaneous Publication No. 287.) The maps include only illustrative species and do not indicate transplants for shade purposes, etc.

The Birch Family

This family includes the birches, alders, hornbeam, ironwood and hazel. Although all cause some pollinosis and the writer has observed positive skin reactions to each, the outstanding member is the birch.

Different species of this family have pollens that may be distinguished on careful study. However, the distinguishing features are so slight that when ob-



Fig. 140.—Pollens. Upper left, black walnut (methyl green); upper right, willow (in saline); lower, black willow (methyl green).

served on the pollen slide identification can usually not be made closer than by family. The features characteristic of the birch family are also found in the Myricaceae (sweet gale), the Haloragidaceae (water-milfoil) and species of certain other families, but these are not of importance in pollinosis.

The grains are smooth, sometimes faintly granular, and contain from three to seven pores approximately equally spaced around the equator. The pores protrude as rounded domes, giving an angular outline. The protrusion is due to thickening or building up of the intine, sometimes also an annular thickening of the exine. See Figs. 143, 147.

Fossil pollen grains of the birch family have been described.



Fig. 141.—Western cottonwood near Dallas. Detail of leaves (right). Note delta shape.

Birch. *Betula* Spp.—The term *betula* is said variously to be derived from *betu*, its Celtic name; from *batuere* (Latin “to beat,” referring to the birch rod with which roman lieters drove back the populace); and, by Pliny, to *bitumen*.

The bark of all members of this genus is characteristically marked with long horizontal lenticels or oval dots. Most of the barks separate in thin papery plates. These characteristics are best seen in white birch but are also present in the red, black and yellow species.

One species of white birch, also called gray or aspen leaf birch (*Betula populifolia* Marsh), found in the New England states and neighboring Canada, possesses a leaf shaped much like that of poplar, with a similar long aspen-like petiole or leaf stem (though not laterally compressed). Like the latter it trembles in the slightest breeze.

Betula papyrifera, Marsh, white birch, paper birch or canoe birch, the common white birch, is distributed over the northern states and into Canada. Red birch, *B. nigra* L. or river birch grows by predilection in moist land. Yellow birch, *B. lutea* Michx. f. is widely dis-

tributed through the East from Canada to North Carolina. Black birch, *B. lenta* L., or sweet birch, also called mahogany birch, has bark with the above characteristics, but is black and shiny like a cherry tree. It is sometimes called cherry birch. The tendency in all varieties for the bark to peel aids in identification. Fig. 144.

The branches have graceful outward curves, drooping downward at the tip with delicate feathering or "spray" of the small twigs giving a delicate lacy appearance. Its gracefulness justifies its appellation, "The Lady of the Woods." It is more slender than the elm. The characteristic spray facilitates recognition of birch, elm and beech in the winter when there are no leaves. The bark enables one readily to distinguish the three from each other.

Pollination occurs relatively early, around April and May, before the leaves unfold.

The birches in general are more abundant in the eastern half of the United States with white and yellow predominating in the North and yellow and black in the South. There is a red birch in California. Figs. 145, 146.



Fig. 142.—Arizona cottonwood in Rio Grande valley near Taos, N. M.

Birch pollen usually contains three germinal pores, occasionally more, up to seven, which protrude, giving the grain its angular appearance. A larger number of pores is often observed in yellow birch where the four pore grains are fairly frequent. Figs. 143, 147.

There appears to be crossed allergic reactivity among all varieties of birch.

Hornbeam, ironwood. *Carpinus caroliniana* Walt.—The wood of hornbeam, blue beech or water beech is very strong and was used for making the yokes which connected the horns of oxen. The name ironwood indicates the toughness of the wood.

It is a tree of the temperate zone, preferring deep moist soil and found abundantly along the borders of streams and swamps through the United States, east of the Rocky Mountains. Fig. 148.

Its bark resembles more that of beech than birch. It is smooth, dark bluish gray instead of the light gray of the beech, and is as popular for the cutting of lovers' initials as the latter. A peculiarity of the trunk is the tendency of the outlines of the branches to appear to run down the trunk giving an irregularly rounded appearance and suggesting a Gothic church column. Its leaves somewhat resemble those of beech.

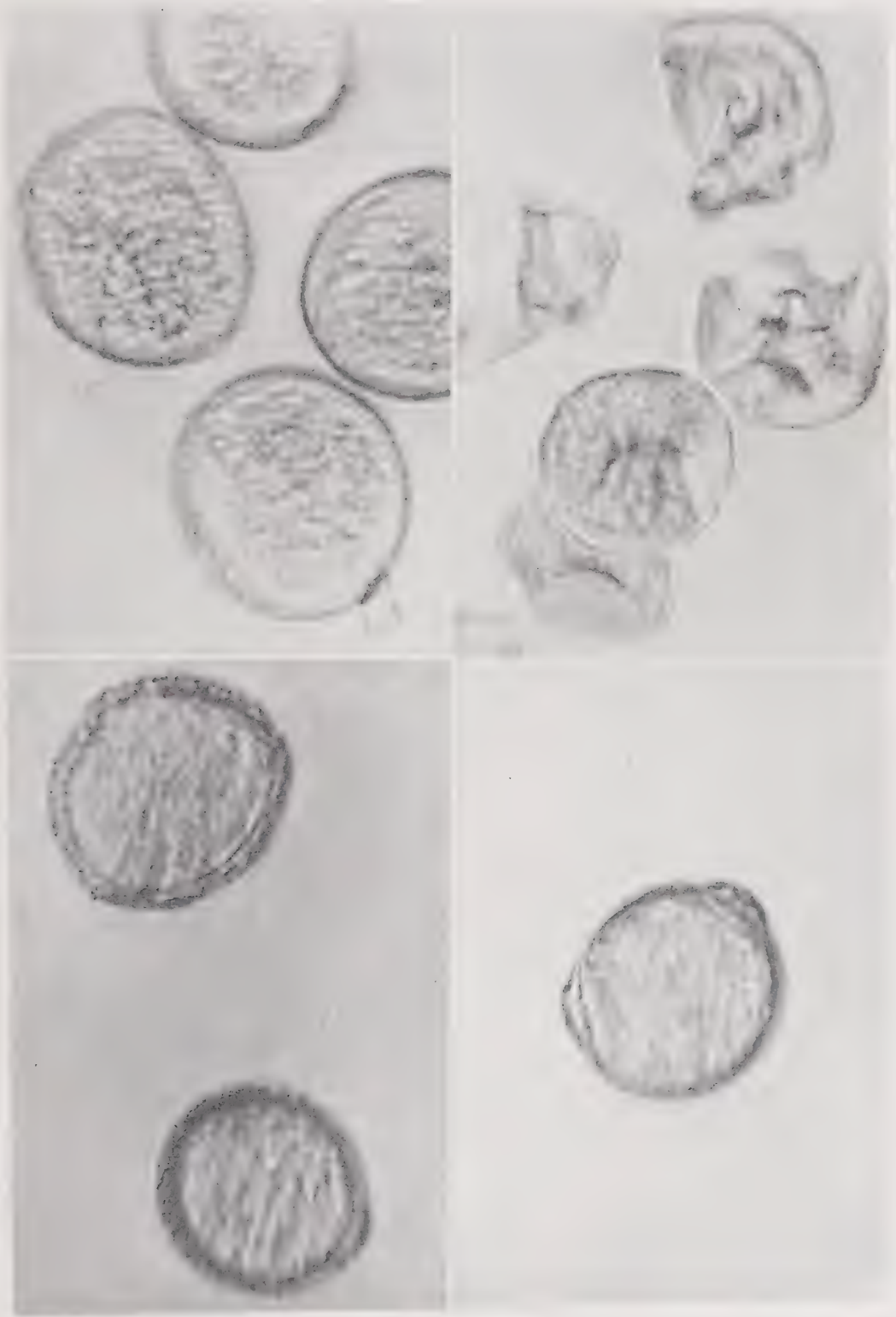


Fig. 143.—Pollens. Upper left, aspen (in saline); upper right, aspen (in oil); lower left, cottonwood (in saline); lower right, yellow birch (in saline). Note the presence of only two germinal pores in this particular pollen grain.

Hop hornbeam, ironwood. *Ostrya virginiana* (Mill.) K. Koch. This is a small slender tree usually found on dry gravelly slopes and ridges and in the shade of larger trees. It ranges throughout the United States east of the Rocky Mountains. Its fruit so closely resembles the common hop-vine as to give rise to its name. Indeed, it is quite a mimic; the fruit resembling hops, the leaf birch, while the spray resembles beech. However, there is individuality in its strength which excels that of all other forest trees. This is so great that it is used by woodsmen as a lever and is sometimes called leverwood. Fig. 149.

Like willow, poplar and birch, it was a prehistoric plant, traces of leaves and fruit being found in fossil remains of Greenland.



FIG. 144.—Birch. Both white birch (left) and yellow birch (right) are easily recognized by the peeling character of the bark.

Carpinus pollen grains are more nearly spherical than those of birch. However, this is not diagnostic. The pores do not protrude as much. This is of some value in identification. Four-pored grains are rather frequent in *Ostrya virginiana*. Fig. 147.

Hornbeam and ironwood are not important hay fever plants, although positive skin reactions have been observed. One cannot be certain that these are not crossed reactions indicating group sensitization to other pollens such as birch.

Alder. *Alnus Spp.*—Native alder is rarely more than a shrub which follows the water courses. It pollinates very early, before the leaves have appeared. Fig. 150.

Alder pollen differs slightly from other members of this family in that there are usually four or more germinal pores as contrasted with the more customary three in the members mentioned above. Wodehouse states that the most distinctive characteristic is the bandlike



Fig. 145.—See legend on page 569.



thickening beneath the exine, extending in curves from pore to pore on each side of the equator. These are best seen in stained material. These bandlike thickenings are not found among other species of the family. Fig. 151.

Alder was an early evolutionary form of the dicotyledonous trees. It is found in the northeastern states to North Carolina and scattered along river bottoms to Florida and Texas.

Alder causes some pollinosis.

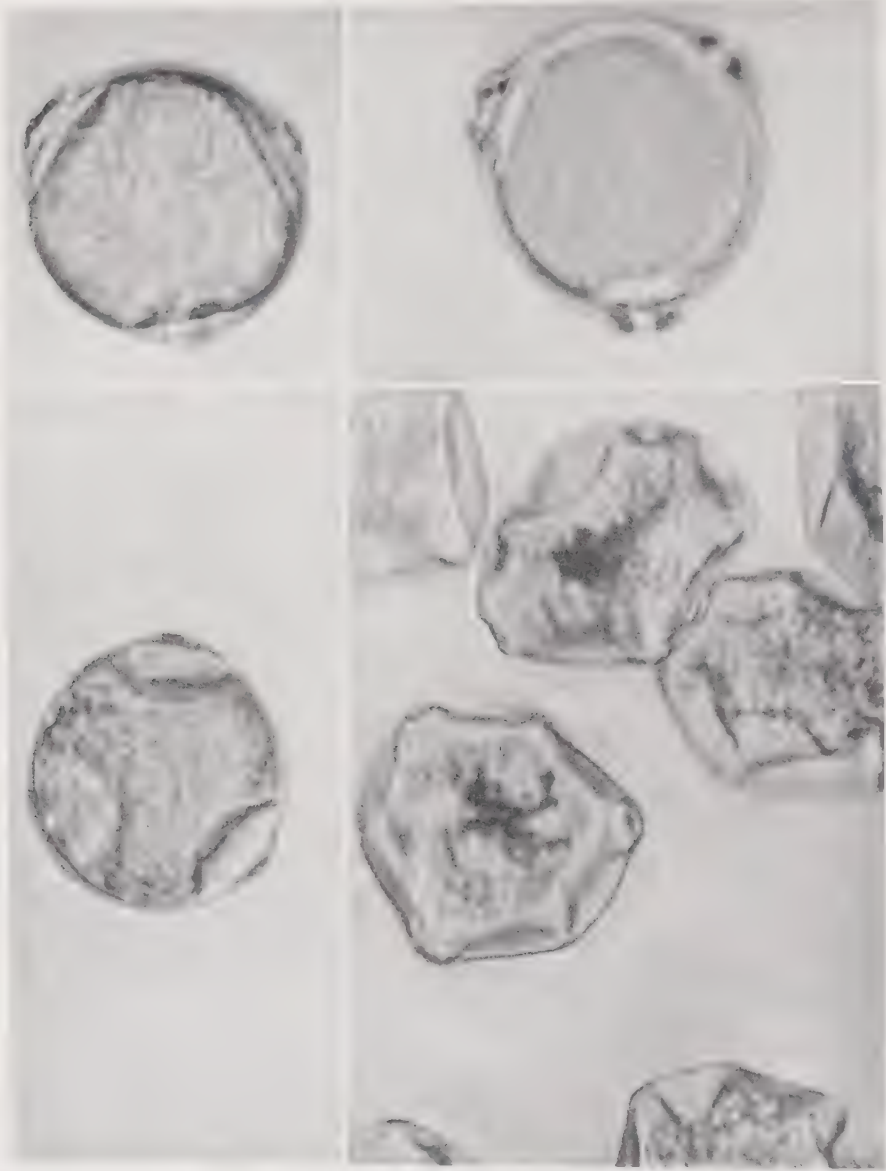


Fig. 147.—Pollens. Upper left, yellow birch (in saline); upper right, yellow birch (in saline); lower left, ironwood (in saline); lower right, ironwood (in oil).

Hazelnut. *Corylus Americana* Walt. Borkh.—This shrub, found in thickets from Maine and Ontario to Saskatchewan, Florida, and Kansas, has not been shown to be of importance in pollinosis. Its pollen resembles that of birch. Fig. 151.

The Beech Family. *Fagaceae*

The name *Fagus* takes its origin from the Greek *phago*, to eat. The botanical name for oak, *Quercus*, considered by most botanists as a member of the beech family, is said to have been derived from two Celtic words meaning a "fine tree."

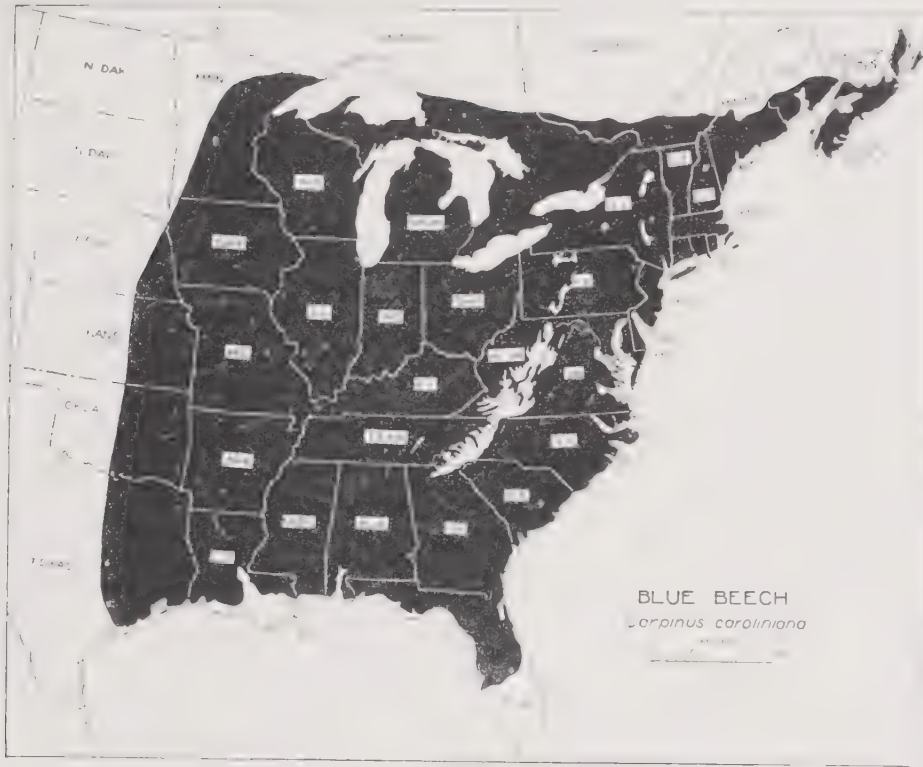


Fig. 148.—See legend on page 569.



Fig. 149.—See legend on page 569.

Beech and oak have many points in common, one of which is that oak and at least young beeches continue to hold their dead brown leaves through the winter. Trees which, during the winter or early spring, still have dead leaves are usually either oak or beech. The latter may be distinguished by the character of the bark which is smooth and grayish. The smaller beech branches are often snowy white, almost resembling snow. The tree has a fine spray, almost as delicate as that of the elm. "Beech forests" develop, first because the tree has suckers and second because the shade is so dense that it is difficult for other trees to flourish. Fig. 157.



Fig. 150.—Alder catkins. These are fully developed before unfolding of the leaves.

There is a tradition that the beech is rarely struck by lightning. This appears to have sound basis in that the tree is rich in fat and a poor conductor of electricity.

Chestnut, *Castanea dentata* (Marsh), a member of the beech family, so resembles the red oak that during the winter the two can scarcely be distinguished. It is insect pollinated in great measure and, owing to the chestnut blight, is becoming a rare tree in the United States. For this reason it is not of material importance in pollinosis.

Oak, *Quercus* Spp.—There are many varieties of oak, the most majestic forest tree, the tree which has been compared with the lion among the quadrupeds and with the eagle among birds.

Its leaves are unlike those of any other tree, are rather thick, shiny, deeply serrated. Even among those oaks in which the leaves are much simpler, as water oak or willow oak, its thickness, glossiness, and persistence through the winter are still apparent.

Catkins usually develop when the leaves are half grown. Figs. 152, 153.

Beech and oak may both cause hay fever. The various species of oak (about 220) shed tremendous quantities of pollen but cause rather less pollinosis than many other trees which produce less pollen.

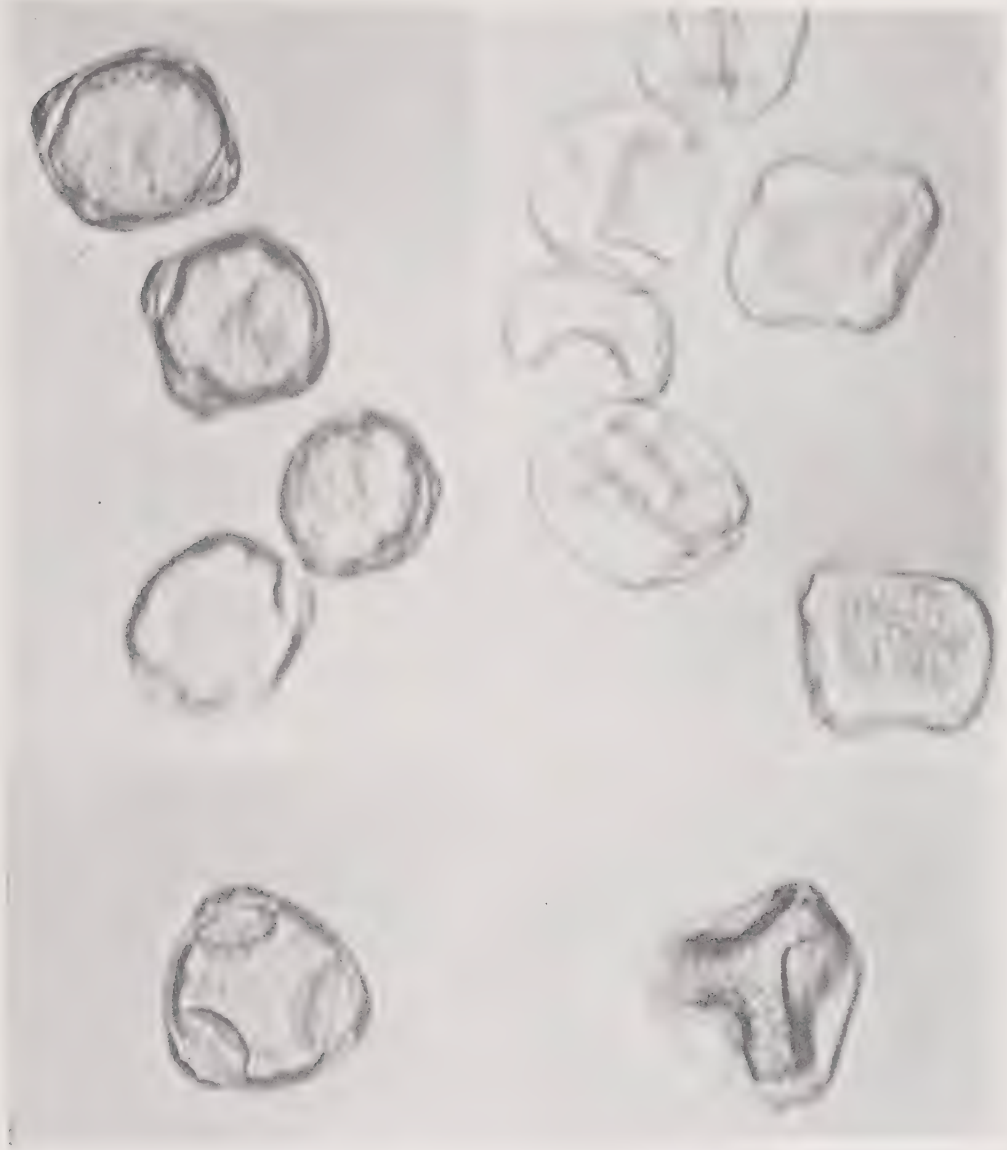


Fig. 151.—Pollens. Upper left, alder (in saline); upper right, alder (in oil); lower left, hazel (in saline); lower right, hazel (in oil).

The outstanding characteristic of an oak pollen grain is the hyaline wedge-shaped plugs imbedded in the cell beneath the furrows. These wedges are usually three in number corresponding to the customary number of furrows. It will be seen from the figure that the oak grain when moist usually has three furrows, displays the hyaline plug, and is spherical in form. When dried it is ellipsoidal with the furrows tightly closed, appearing as shallow grooves. Figs. 155, 156.

There is one special characteristic of oak and beech pollen which unfortunately does not appear in dried specimens. When moist, the germinal furrow protrudes to such an extent that there is a rupture which allows the gelatinous cell content to extend outward from the pollen grain.



Fig. 152.—Oak. Winter identification is facilitated by the fact that the dead leaves stay on the branches through the cold months.



FIG. 153. Oak catkins. In some species (upper) these appear before unfolding of the leaves; in others (lower), at the same time.

Differentiation of the various species of oak pollen is unsatisfactory. However, this is not a matter of importance in allergy since all appear to cross react.

California live oak is said by Selfridge to be an important hay fever tree in California; by Rowe to be relatively unimportant. There are 14 species of oak in California alone.

Beech. *Fagus grandifolia* Ehrh.—The pollen of beech is very similar to that of oak. The hyaline bodies are more nearly spherical and the grains when moistened suffer less distortion due to gaping of the furrows. Many grains of some of the species show but two furrows. The exine is more coarsely and more constantly roughened.



Fig. 154.—See legend on page 569.

The Elm Family. *Ulmaceae*

This is considered by some to be a member of a larger group, the nettle family or urticaceae. Britton and Brown separate the two groups, including elm and hackberry in the former and the nettles in the latter. Wodehouse groups all together also including mulberry.

Elm. *Ulmus Americana* L.—The elm may be easily recognized in winter, the branches spreading outward as continuations of the trunk, like the fingers of a partially opened hand, arching gracefully until at their extremities they come to point, slightly, toward the ground. The continuousness of the arch of the branches is most characteristic. The fine interlacing of small branches in the spray when the leaves are gone is so delicate as to suggest filigree network.

Elm is abundant in moist woods through the entire North. White elm and silver maple are usually the first trees to come into flower in the early spring in the East. Pollination occurs before unfolding of the leaves, in the latitude of Virginia in February, farther north in March.

The elm blossom is a complete flower and possesses no catkins. It is very small and usually seen only by those who seek it. See Fig. 159. The leaves may be recognized by the unequal base, one side being larger than the other.



Fig. 155. Pollens. Upper, white oak (in saline); lower left, red oak (in saline); lower right, red oak (in oil). Note hyaline wedge-shaped plugs embedded in the cells.

There are about 16 species of elm in the northern hemisphere, the two most important in the United States, besides the American elm, being corky elm, *Ulmus Thômasi*, Sarg., in the northeastern states and winged elm, *Ulmus alata* Michx., in the southeastern states. Fig. 148. In various parts of the South, and particularly in Northern Texas, the *Ulmus crassifolia* blooms in September at the same time as the ragweeds, and is a serious complicating factor at that time.

Wodehouse describes the pollen as spheroidal or oblatelly flattened, entirely lacking germinal furrows but provided with two to seven pores, equatorially arranged. The grains are very simple with little or no sculpturing. When partially dried the germinal pores are scarcely visible, although they may be seen in moistened preparations. They are usually from three to seven in number, most often five, giving a pentagonal appearance to the moist grain. There are no thickenings around the pores. Exine is smooth. Fig. 161.

Elm pollen is abundant, and an important factor in tree pollinosis.



Fig. 156.—Pollens. Upper left, water oak (in saline); upper right, water oak (in oil); lower left, jack oak (in saline); lower right, beech (in oil).

Hackberry. *Celtis occidentalis*, L.: *Celtis Mississippiensis*, Bosc.—This tree causes some pollinosis especially in the Mississippi Valley and in Texas where Kalm states that it is an important factor in the region of San Antonio. It is a member of the elm family and when fully grown (height to 120 feet) it resembles elm in appearance, in the pose of its trunk, the sweep and fall of its branches, and the effect of its foliage mass. Close inspection, however, shows a small fruit or berry, a drupe, from one-half to three-fourths inch long, tipped



FIG. 167.—Beech. The center tree is smooth barked, light gray, the tree on which children love to carve their initials. Dead beech leaves sometimes remain attached to the branches through the winter.

with the remnant of a style, which ripens in September and October, and remains on the branches during the winter, Figs. 162, 163. It is quite abundant in the Mississippi Valley, much less so east of the Alleghenys and rare west of the Rockies. Bowie (1938) reports large atmospheric pollen concentrations in the neighborhood of Nashville, Tennessee.

The name, *Celtis*, indicates that it is supposed to have been known to the ancient Celts.

Trees in the eastern United States are more scrubby and do not resemble the elm as closely. According to Thommen the most important hay fever species is *C. Occidentalis*. Pollination is in April and May, soon after the leaves appear.

Wodehouse states that the pollen varies greatly in size, from 25 to 55 microns in diameter, and the pores range from 3 to 10 or more. Usually there are more than 3. The pores exhibit no regularity of arrangement or size, 2 or 3 sometimes appearing to coalesce. The larger the grain, usually the larger the number of pores. Pores are not perceptibly raised above the surface of the grain and the subexinous thickenings are not pronounced. There is slight thickening around the germ pores. Fig. 161.



Fig. 158.—Elm. Winter recognition is facilitated by the slender graceful curve of the branches, rather continuous with the trunk, giving the impression of spreading fingers extending from an upraised hand. Since those illustrated are small they do not show the graceful spray or arch. Right, winged or corky elm is recognized by the corky irregular ridges present on branches over 2 years old.

The Mulberry Family. *Moraceae*

This, like elm and hemp, is placed in the nettle family by Wodehouse. It will be recalled that among the foods this family includes mulberry, fig, and hop.

Of the three chief varieties, red, white and black, red is indigenous to America. Its leaves are characteristic of the family, being sometimes heart



FIG. 159.—Characteristic flower of the elm.



FIG. 160.—See legend on page 549.



Fig. 161.—Pollens. Upper left, American elm (in saline); upper right, American elm (in oil); lower left, hackberry (methyl green); lower right, true mulberry (methyl green).



Fig. 162.—Hackberry in Dallas. General resemblance to elm tree is evidenced.



Fig. 163.—Hackberry. Left, warty trunk. Right, berry which remains on through the winter and provides ready differentiation from elm.



Fig. 164.—See legend on page 569.

shaped, sometimes lobed and often mitten shaped, asymmetrical. The silkworm thrives well on the white mulberry but not at all on the native red since the leaves are too thick and rough even when young, to provide proper food.

Black mulberry, *Morus nigra* L., is one of the oldest cultivated trees. It lives to a ripe age. A mulberry at Cambridge, England, said to have been planted by Milton, is still living. The tree was introduced into England in 1505 for sericulture, but the silkworm does no better on its leaf than on the red.

White mulberry, *Morus alba*, L., preferred by the silkworm, is native of China, widely cultivated in the eastern Mediterranean.

Red mulberry, *Morus rubra*, is found east of the Mississippi and in the first range of states west thereof. White and black mulberry are found only where introduced by cultivation and are not at all abundant.



Fig. 165.—Paper mulberry. Left, a common tree in Petersburg, Va. Right, detail of leaves and catkin.

Paper mulberry. *Broussonetia papyrifera* (L.) Vent.—Although a member of the same family, this is of a different genus and the chief pollinosis excitant in the group. It is called paper mulberry because, in Japan, the young shoots are used for paper manufacture. In many islands of the Pacific the young shoots are pounded together to make a material used for clothing.

This tree, like the white mulberry, was widely introduced along the Atlantic seaboard in colonial days for sericulture. The silkworm industry did not flourish but the tree did. As a consequence, it has become a popular lay fever tree in the early settlements such as Washington, Williamsburg, Petersburg and on south to Charleston. It has been widely planted elsewhere as an ornamental tree and may be found from New York to the Gulf States, Missouri and Oklahoma. The tree is dioecious, stamens and pistils being found on different trees. Most of the cultivated paper mulberry is staminate, catkin bearing. Pollen is locally abundant and extremely toxic, causing a form of pollinosis which is difficult to control. Figs. 165, 168.

The pollen grains are so small that their delivery into the air would be difficult were it not for a special mechanism. As the anther opens the filament of the stamen uncoils, like a spring, scattering the pollen. This occurs explosively and justifies its description during pollination as "the smoking mulberry." The clouds of discharged pollen are easily seen.



Fig. 166.—Pollens. Upper left, paper mulberry (in saline); upper right, paper mulberry (in oil); lower left, sheep sorrel (methyl green); lower right, yellow dock (in oil).

Pollen is small, thin walled, devoid of sculpturing. There are usually but two germinal pores. However, on the pollen slide it appears as a shriveled miniature grass pollen and is best recognized by its size and its occurrence in the proper pollinating season. This is around June. Figs. 161, 166.

The Buckwheat Family. *Fagopyrum Esculentum*

Curly dock. *Rumex crispus* L.—**Sheep sorrel.** *Rumex acetosella* L.—The two important groups in this family as far as pollinosis is concerned are the sorrels and the docks. These weeds are of the genus *Rumex*. The members of chief importance are sheep sorrel (*Rumex acetosella*) and narrow leaf or yellow or curly dock (*Rumex crispus*). Both are widely distributed through the United States, and are wind pollinated. The former sheds large quantities of pollen in June and July during the grass season while the latter sheds comparatively little. They have been mentioned more frequently as of importance in the West than in the East, although the former is rather widely distributed over the eastern and central states.



Fig. 167.—Cockerbur. Photographed at Galveston.

The pollens of both species show few characteristics by which they may be identified. They are smooth, with very indistinct germinal furrows which allow infolding when dry. When seen dry, as on the pollen slide, they very much resemble grass pollen. The exine is rather coarsely pitted but this is not easily distinguished in the dry state. There are usually four furrows in *Rumex acetosella*, three in *Rumex crispus*. The latter pollen is slightly larger than the former. *Rumex acetosella* pollinates during the grass season and is rather widely distributed over the eastern and central states. Figs. 167, 168, 169.

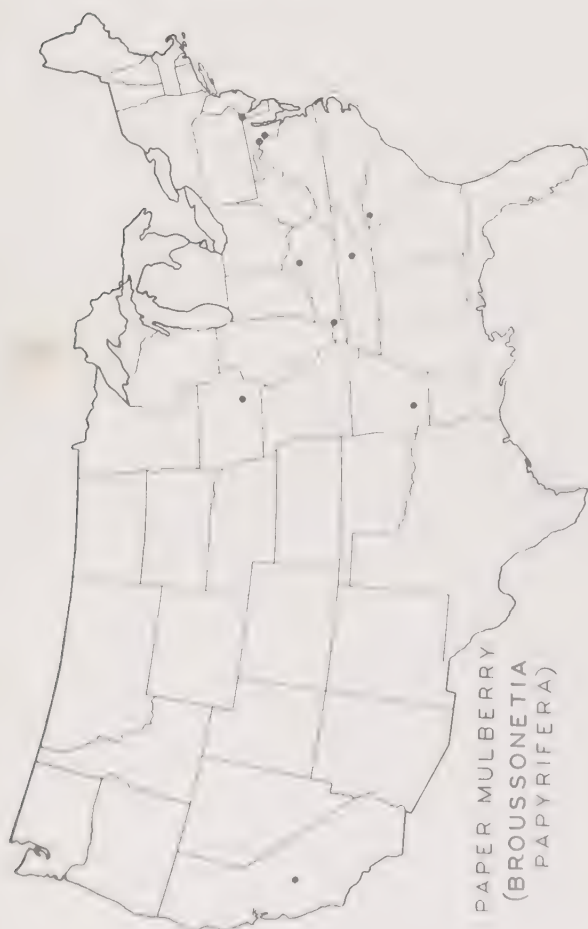


Fig. 168.—See legend on page 545.



Fig. 169.—Pollens. Upper left, narrow leaf dock (in saline); upper right, narrow leaf dock (in oil); lower left, lamb's-quarters (in saline); lower right, lamb's-quarters (in oil).

Note the suggestion of dimpling, as in a dimpled golf ball, at the periphery of lamb's-quarters in oil.

The Goosefoot Family. *Chenopodiaceae*

Members of this and the amaranth families are often considered together in a larger group, the order chenopodiales. There are many points of resemblance between the two families.

The pollens of species of both families are scarcely distinguishable by examination on the pollen slide. In general, they are spherical, resembling a



Fig. 170.—Lamb's-quarters.



Fig. 171.—Lamb's-quarters in habitat.

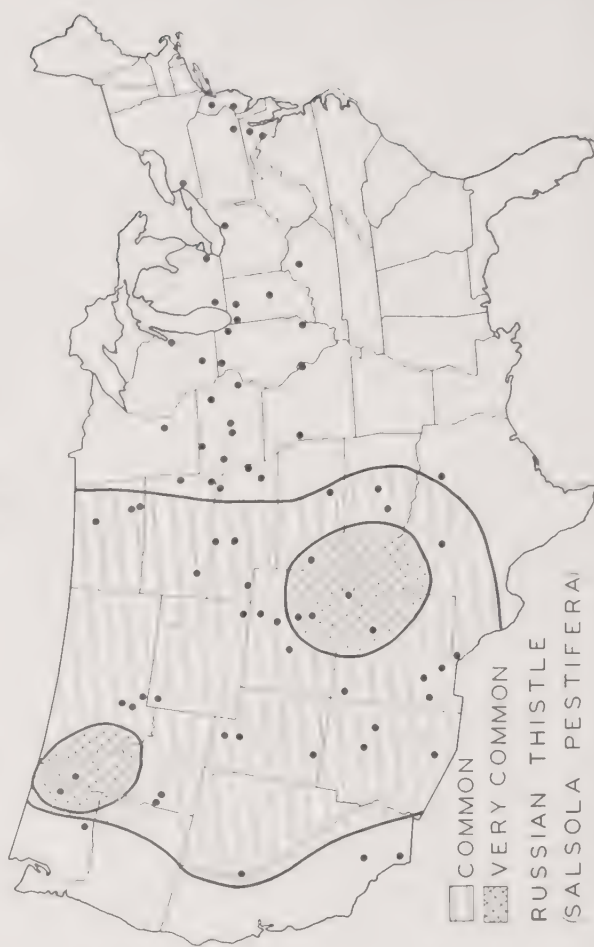
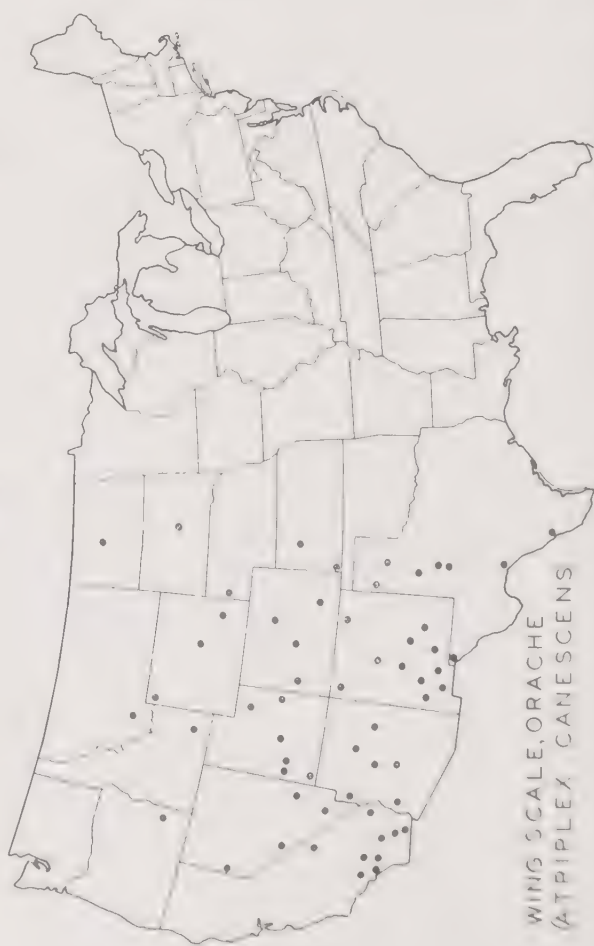


Fig. 172. See legend on page 545.

dimpled golf ball in appearance, due to an extremely large number of germinal pores, marking the sites of the numerous surface depressions. Germinal furrows do not show at all. According to Wodehouse these pores represent evolutionary



Fig. 173.—Kochia.

remains from that time when these plants were entomophilous and the exine was heavily sculptured. Characteristic of the change of anemophily the sculpturing has disappeared and the exine has thinned, but the pores remain. In view of



Fig. 174.—Shadscale, saltbush.



Fig. 175.—Russian thistle, near Glasgow, Montana.



Fig. 176.—Russian thistle, Badlands, North Dakota.

their great number one would logically anticipate that they replace germinal furrows in the function of allowing for change in size with acquisition or loss of moisture. This probably does occur to a limited extent, but with pronounced drying, as on the pollen slide, there also occurs an infolding, a convacity on one side. (See Fig. 177.)

There is some difference in the surface characteristics of the various species but not enough for identification. Thus the pollen of Russian thistle (*Salsola pestifer* A. Nels) shows unusually large pores with wavy margins and a more granular exine, giving the grain a more rugged appearance than that of others.

Lamb's-quarters. Goosefoot. *Chenopodium album* L.—The shape of the lower larger leaves, somewhat resembling that of a goose's foot, explains the name popularly given to the family. The upper narrow leaves do not possess this resemblance. This plant is widely distributed, and flowers in late summer. It is of little importance in the East, much more so in the western half of the United States. Figs. 168, 169-171.

Mexican tea. *Chenopodium ambrosioides* L.—In spite of its name this weed grows widely through the United States and Canada. One variety provides oil of chenopodium, an anthelmintic. The weed flowers late in summer and is a minor cause of hay fever. Fig. 172.

Burning bush. *Kochia trichophylla* Stapf.—This is an ornamental plant introduced from Europe and Asia, extensively grown in the United States, which has escaped from cultivation especially in the West where it has become a troublesome weed and a cause for much hay fever, especially in the western plains area. Figs. 173, 177.

Orache. *Atriplex* L.—There are several species causing considerable pollinosis in the Rocky Mountain states, especially Arizona and to a slight extent in California. These include *Atriplex Wrightii* S. or annual salt bush, and *Atriplex canescens* (Pursch.) Nutt., wing scale, often also called shad scale. Figs. 172, 174.

Another species of *Atriplex* is the familiar sugar beet, *Beta vulgaris* L., which is wind-pollinated and which, according to Dutton,* causes pollinosis among those near El Paso who work in the beet growing industry.

Greesewood. *Sarcobatus vermiculatus* (Hook) Torr.—This grows in the arid regions of the West, especially western Texas and neighboring states and as far north as Washington. It derives its popular name from the fact that the wood and especially the root is oily, making good firewood. It flowers in later summer, is wind-pollinated, and sheds rather large quantities of pollen which causes some pollinosis.

Russian thistle. *Salsola pestifer*, A. Nels.—This is not a true thistle, its resemblance being that it possesses thorns and becomes a tumbleweed. It is said to have been imported with Russian wheat into the wheat growing areas of the West and has become a troublesome weed in that section. In its early growth it is a grass-like plant, relished as forage. About midsummer the stem becomes hard, greatly branched, the leaves fall away and are replaced by spines. Late in summer it breaks away at the base, becoming a tumbleweed, easily blown long distances by the wind, scattering seed along the path of its progress and usually ending up against fences, railroad rights of way, etc. See Figs. 172, 175, 176, 177.

It pollinates in late summer, shedding large amounts of highly toxic pollen, causing much pollinosis in the western states, especially in the plains area.

The Amaranth Family. *Amaranthaceae*

The Pigweed Family

As previously stated, the pollens of the amaranths and chenopods are indistinguishable, all resembling dimpled golf balls, due to the presence of large but variable numbers of germinal pores. Two genera of the family, *Amaranthus* and *Aenida*, are responsible for much pollinosis in the West.

Redroot pigweed. Rough pigweed. *Amaranthus retroflexus* L.—The amaranths are careless weeds, also known as pigweeds, and widely distributed through cultivated areas of the

*Dutton, L. O.: Personal communication.



Fig. 177.—Pollens. Upper left, *kochia* (methyl green); upper right, sugar beet (in oil); lower left, Russian thistle (in saline); lower right, Russian thistle (in oil). Note dimpling throughout.



Fig. 178.—Rough pigweed.

United States, especially in neglected gardens. Members of the family are of little importance in the East, rather more in the West, especially in the states bordering Mexico—western Texas, Arizona, New Mexico and southern California, where Palmer's amaranth is of considerable importance. It flowers from August to October, shedding relatively small quantities of pollen. Figs. 178, 181.

Palmer's amaranth. *Amaranthus palmeri* S. Wats.—Common in moist ground, it is found chiefly from Kansas to Colorado, in California and extending southward through the state into adjacent Mexico. Pollination occurs from June to September.



Fig. 179.—Western water hemp.



Fig. 180.—Pollens. Upper left, spiny amaranth (in saline); upper right, spiny amaranth (in oil); lower left, western water hemp (in saline); lower right, western water hemp (in oil). Note dimpling.

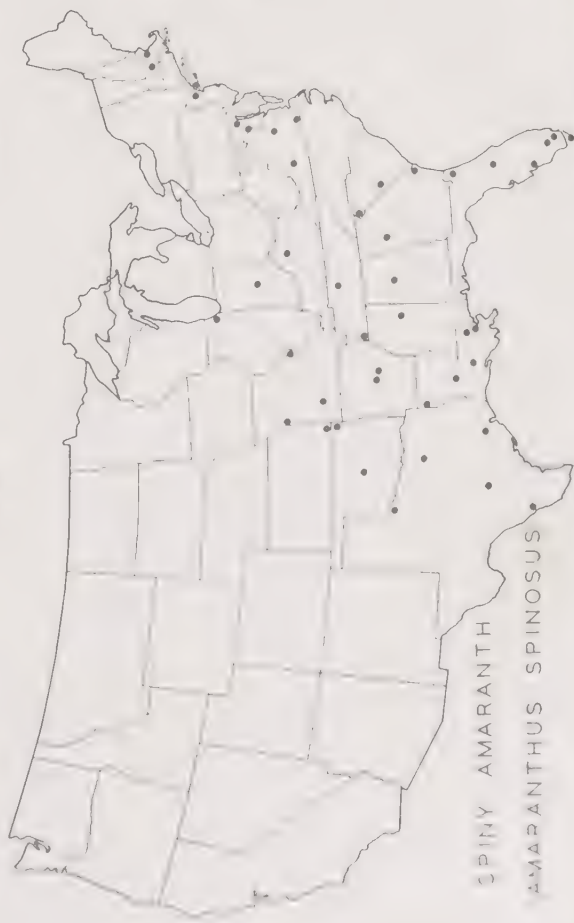
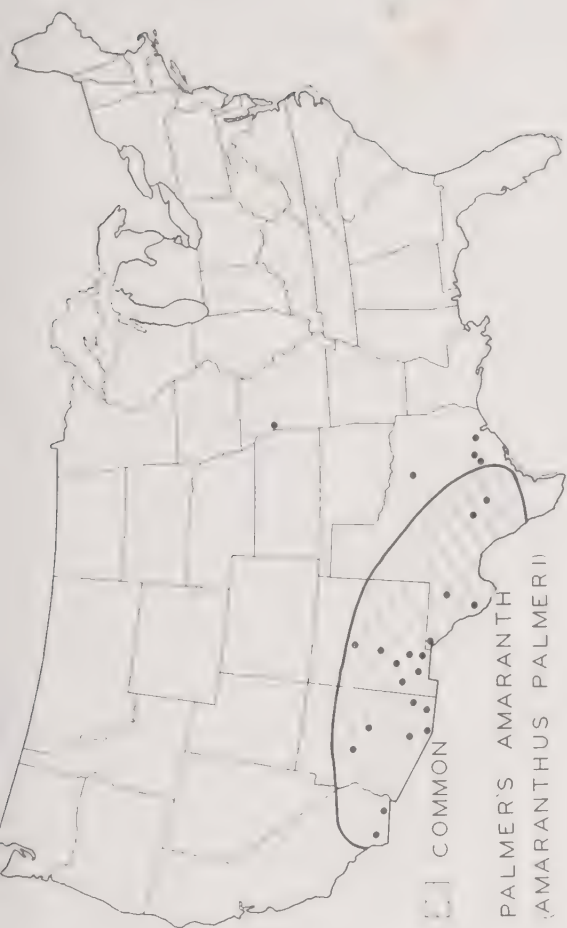


Fig. 181.—See legend on page 545.

Spiny amaranth. *Amaranthus spinosus* L.—This plant is common throughout the United States and neighboring areas of Canada and Mexico. It pollinates heavily from June to September and is a major pollinosis factor in essentially the same territory as that for Palmer's amaranth. Figs. 180, 181.

Tumbleweed. *Amaranthus graccizans* L.—Like *Amaranthus retroflexus* this is a common weed throughout North America. It sheds relatively little pollen and is a secondary factor in the Rocky Mountain and Pacific Coast areas. Pollinating period is July to September. Fig. 181.

Western water hemp. *Acnida tamariscina* (Nutt.) Wood.—Rather widely distributed through the plains area this is especially important in Oklahoma where, according to Balyeat, it is responsible for symptoms in 35 per cent of hay fever cases. Pollination is from July to September. Figs. 179, 180, 194.



Fig. 182.—Sycamore and sweet gum. Left, buttons remaining on the buttonwood or sycamore through the winter. Right, seed vessels of the sweet gum.

The amaranth group in general pollinates from July to September and is a factor of some importance in the southwestern states, Idaho, Montana and the mountain or eastern section of Oregon and Washington. Palmer's amaranth, spiny amaranth and western water hemp appear to be the most important allergenic members.

The Witch Hazel Family. *Hamamelidaceae*

Sweet gum. *Liquidambar styraciflua* L.—This is classed by some in the witch hazel family, by others in the Altingia. We have observed positive skin reactions to it but have

not found it necessary to desensitize. Sweet gum is a large tree with resinous sap, the wood of which is rather widely used in cabinet work. It is found in woods from Connecticut and southern New York to Florida, Illinois, Missouri, Texas and Mexico. It is also found in Central America. Pollination occurs in April and May. Its wind borne pollen is abundant, never seen on slides and therefore requires identification. It is spheroidal, containing from



Fig. 183.—Sycamore. Detail of the bark, showing tendency to peel off in plaques.



Fig. 184.—The buttons or seed vessels of sycamore (left) and sweet gum (right). Since these remain attached through the winter they facilitate winter recognition.

12 to 20 circular pores of varying size, distributed quite evenly over the surface. When moist the pores bulge, indicating their function of adjusting to change in size. They are not as noticeable in dried specimens.

The tree is also known as the star-leaved gum because of the star-shaped, five-pointed leaves, somewhat resembling those of sugar maple. It is easily recognized in the winter

because of the fruit balls which hang on long stems. The bark of the small stems is attached edgewise in places, giving a roughness which accounts for another of its names, "alligator tree." Flowering occurs when the leaves are half grown.

See Figs. 182, 183, 184, 185.

The Plane Tree Family. *Platanaceae*

Sycamore. Plane tree. Buttonwood. *Platanus occidentalis* L.—This tree is common throughout the United States, especially from Maine to Iowa and south to Georgia and Texas. The Oriental variety is cultivated in several of the western states. The name *platanus*, derived from *platus*, broad, refers to the shape of the leaf.



Fig. 185.—See legend on page 569.

The tree may be easily recognized in winter because of two distinguishing peculiarities: its bark and its buttons, or fruit balls. The sycamore "casts its bark as well as its leaves." The bark is rigid, lacking the expansive capacity of most other barks. As the tree grows, great flakes drop off, leaving characteristic mottled greenish white and gray smooth surfaces by which the tree may be recognized from afar. The spots sometimes appear as if white washed.

The seed balls or buttons swing from the branches through the winter. Toward spring they break up, liberating many little nuts each with a tuft of rusty wool rather suggestive of dandelion seeds.

Waring and Pope have observed that patients who are allergic to the pollen of cottonwood may also be allergic to the "cotton" of the buttonwood, the wooly tufts attached to the seeds. In Germany, hay fever and asthma have been attributed to the fine hairs of the under surface of the leaves.

Pollen is shed around May, is wind-borne and abundant. It is a minor cause of pollinosis. When moist it is seen to possess three, occasionally four, symmetrically placed germinal furrows. When dried, as seen on the pollen slide, the furrows are drawn deeply inward giving a deeply indented ellipsoidal shape, rather resembling the grasses, but differing in that the surface, the exine, is finely pitted, with a rough reticulate appearance.



Fig. 186.—Pollens. Upper left, sweet gum (in saline); upper right, sweet gum (in oil); lower left, cultivated sycamore (in saline); lower right, cultivated sycamore (in oil).

The Rose Family. *Rosaceae*

The apple family (*Malaceae*) and the peach family (*Amygdalaceae*) are grouped with the rose family in a single higher order, the *Rosales*. In all of these the pollen very much resembles that of *Platanus* just described. Pollen specimens often show linear infoldings similar to that illustrated for date palm, Fig. 111.

Rose, apple and peach pollens, with other members of the families, are strictly insect carried and are not responsible for endemic or epidemic pollinosis. They are usually not seen on pollen slides. However, they are responsible for sporadic cases due to cut flowers in rooms, climbing flowers outside homes, or exposure in gardens or orchards. My experience differs from that of Wodehouse who has observed only two cases of pollinosis due to rose in over 2,000 cases. We have found 18 positive rose reactions and 1 positive apple reaction per 100 positive short ragweed reactions. In the majority of instances further observation

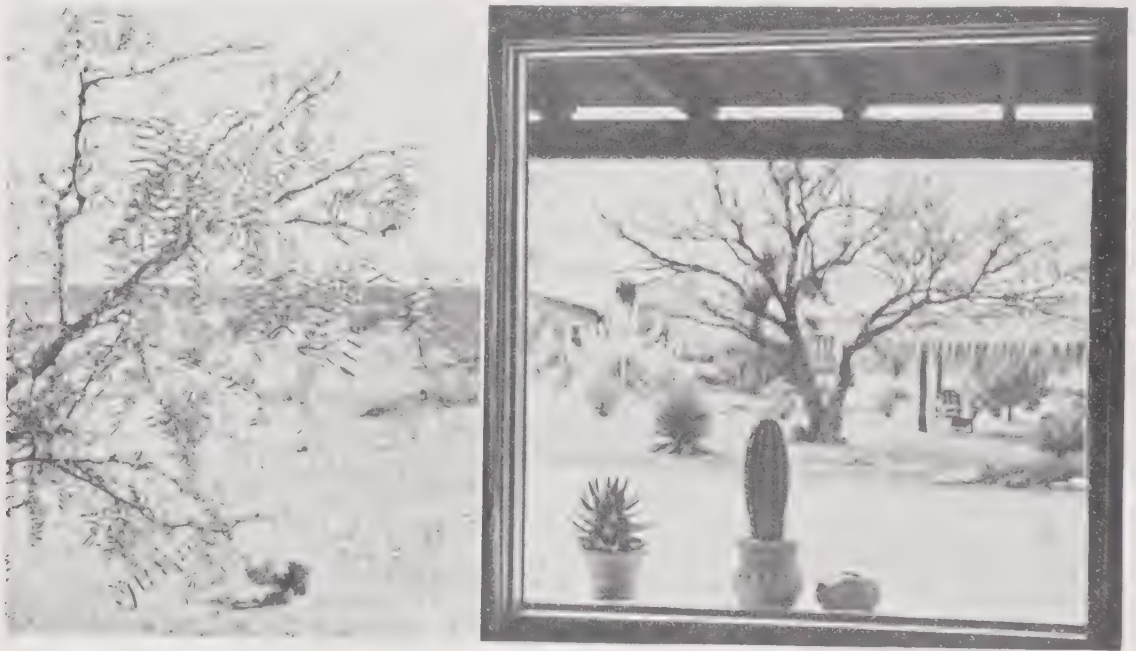


Fig. 187.—Mesquite. Growing as a small bush in the arid regions of western Texas (left) it becomes a sizable tree in the more moist areas of eastern Texas, and in arid regions where sufficient moisture is provided artificially. The above picture, right, was taken near Nogales, Mexico.

has confirmed the etiologic significance of these reactions. They have usually occurred in persons allergic to other air-borne pollens which were responsible for major symptoms, but who found that roses in the house also caused symptoms. We have observed one apple allergic who did not react to any other pollen, who experienced symptoms only when his apple trees were in bloom.

The Mimosa Family. *Mimosaceae*

This family with the senna family (*Caesalpinaceae*) which contains the redbud or Judas tree, honey locust and Kentucky coffee tree; and the pea family (*Fabaceae*), containing clover, alfalfa, lespedeza, all three of which may cause sporadic pollinosis, and the locust tree or bastard acacia (entomophilous and not shown to cause pollinosis); are all closely related and sometimes included as subfamilies in the *Leguminaceae*. In all, the seeds develop in pods.

The immediate members of the mimosa family of interest in pollinosis are mimosa, acacia and mesquite. They are entomophilous but wind-borne to some extent, since the pollen may be observed on slides.

A characteristic of the pollen is that it tends to form in compound grains, groups of four or multiples of four. Acacia pollen usually has 18 cells, rather



Fig. 188.—Mesquite. Details of leaves and thorns. Note resemblance to mimosa-acacia.

squared in appearance, flattened in one direction giving a lens-shaped configuration. Both the individual cells and the group cells are rather squared, producing a striated or gridiron appearance to the group. An exception is seen in mesquite pollen which is usually unicellular, spheroidal, with three long tapering furrows, equidistant, and with a slight bulge at the middle of each furrow, indicating the germinal pore.

Mesquite. *Prosopis glandulosa* Torr.—This has been reported by Sellers as an important cause of pollinosis in Texas. In the discussion of the grasses we observed how mesquite



Fig. 189.—Cat's claw (*Acacia greggii*), a member of the mimosa-acacia family, not yet shown to cause allergy. Note resemblance of leaves to mimosa and mesquite; note pod, as in other legumes, and clawlike thorns.

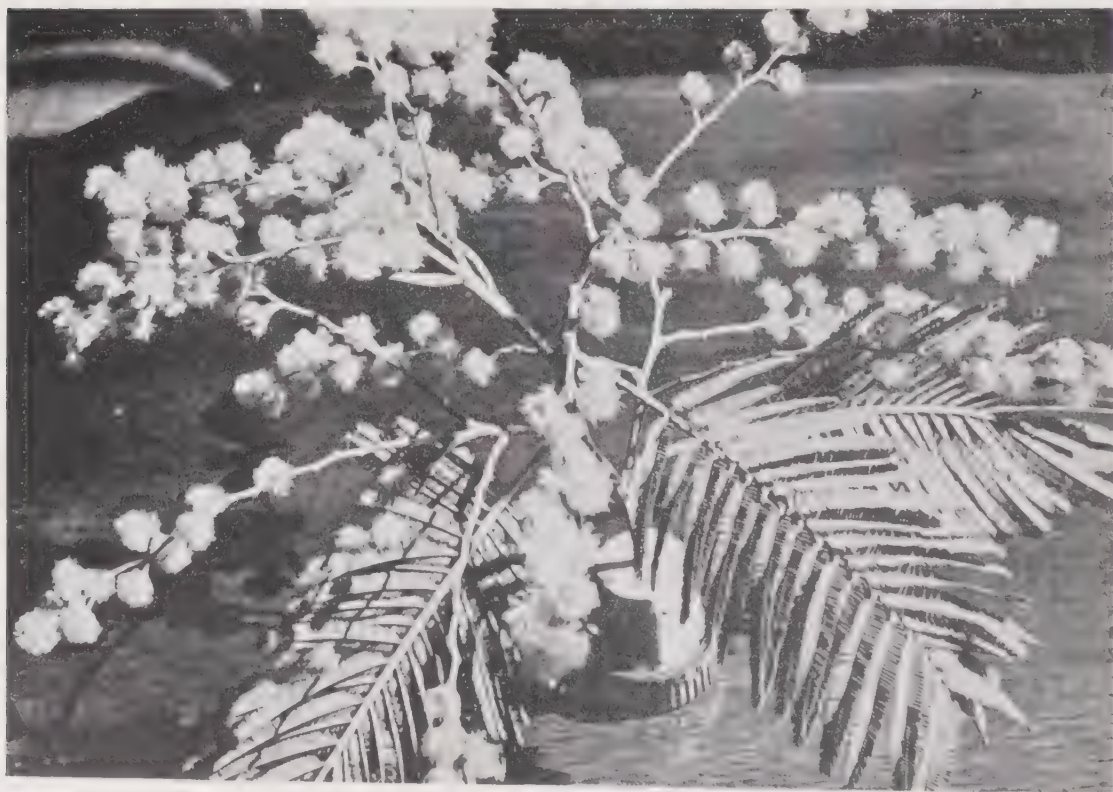


Fig. 190.—Acacia in flower at Berkeley, California. This is an especially toxic pollen for those allergic to it, but since it is not anemophilous, few are affected.



Fig. 191.—Varieties of mimosa and acacia. In general, mimosa (causing sporadic pollinosis, especially in the Southeast) has smaller leaves, while acacia (responsible for some sporadic cases in the Far West) has larger leaves. However, the close interrelationship is indicated in the last figure, showing both types of leaves on the same branch. The writer finds evidence of crossed reactivity to the two pollens.

is becoming more abundant in Texas since the disappearance of grass. There is a point of general interest in its natural history. Where moisture is scant, the roots extend deeply underground while the portion above ground appears merely as a low shrub. Where moisture is abundant the roots do not extend as deeply and the portion above ground develops into a tree of respectable size. In the western portion of Texas, around El Paso, it is a scrubby bush showing little superficial resemblance to its tree form nearer San Antonio. Local tradition has it that in either locality it is the same size except that in the dry sections most of it is underground. Pollination occurs in May, June and July.

See Figs. 177, 178, 179, 193, 194.

Mimosa. Acacia. *Acaciella hirta* (Nutt.) Britton and Rose.—There are a number of varieties, chiefly cultivated as ornamentals. Those near habitations are chiefly responsible for pollinosis, since pollen is not carried far. Acacia is quite abundant along the Pacific Coast especially in California, while mimosa is often found on lawns in the East, especially the southeastern states. The close family relationship is seen in those species which bear both acacia and mimosa type of leaves on the single tree. It is said that such young plants may eventually develop in either direction, "becoming either acacia or mimosa."

In the Southeast we find mimosa responsible for sporadic cases, usually from exposure to a tree on the lawn or near the bedroom window. Rowe* states that acacia may cause hay fever and asthma in certain cases. At times the pollen is extremely toxic. The date of flowering varies in different sections and with different species. It occurs as a rule in the early spring.

See Figs. 190, 191, 192, 193.



Fig. 192.—Mimosa, outside a bedroom window, at Charlottesville, Virginia. Its use as an ornamental and its frequent proximity to homes account for occasional sporadic cases of pollinosis.

The Maple Family. *Aceraceae*

This family contains but one genus with something over 100 species. There are 19 species in North America, the important ones from the viewpoint of pollinosis being the early maples, silver and red, and "ash leafed maple" or box elder. Maple is not a catkin-bearing tree and with the exception of box elder the pollen is primarily insect-borne but considerable pollen does get into the air and appears to be a secondary factor in pollinosis. Positive skin reactions have been observed and the writer has found it at times necessary to desensitize against maple.

Some maples pollinate early in February, in March or in April before the unfolding of the leaves; others during this process; and some later, in June. A maple-allergic may therefore have symptoms over a rather protracted time interval.

*Rowe, Albert H. Personal communication.

Maple. *Acer Spp.*—Maple pollen usually shows three furrows, sometimes more, often asymmetrical. Exine is distinctly granular, the granules being arranged in rows, giving a striate appearance.

Sycamore maple pollinates late, in June, after the leaves have become fully developed. Norway maple also pollinates in June. Red maple, a tree of the eastern half of the United States, flowers before the appearance of leaves, in February, March or April. Silver maple pollinates early, from February to April, sugar maple slightly later, in April and May.



Fig. 193.—Pollens. Upper left, mesquite (methyl green); upper right, acacia (methyl green); lower left, alanthus (methyl green); lower right, box elder (methyl green). Note that while the methyl green stain facilitates direct study through the microscope, it cannot photograph as well as saline and oil preparations.

Maple and elm pollen usually introduce the tree pollinating season in the East. This tree is not of importance in pollinosis in the western half of the country.

Rudolph and Cohen have reported sensitization to maple leaves. This was in a child allergic to several foods, to ragweed and to some of the grasses, whose symptoms persisted after termination of the ragweed season. It was observed that he had trouble especially when in the yard where the leaves were falling. He was tested with Coca's fluid extracts of oak,

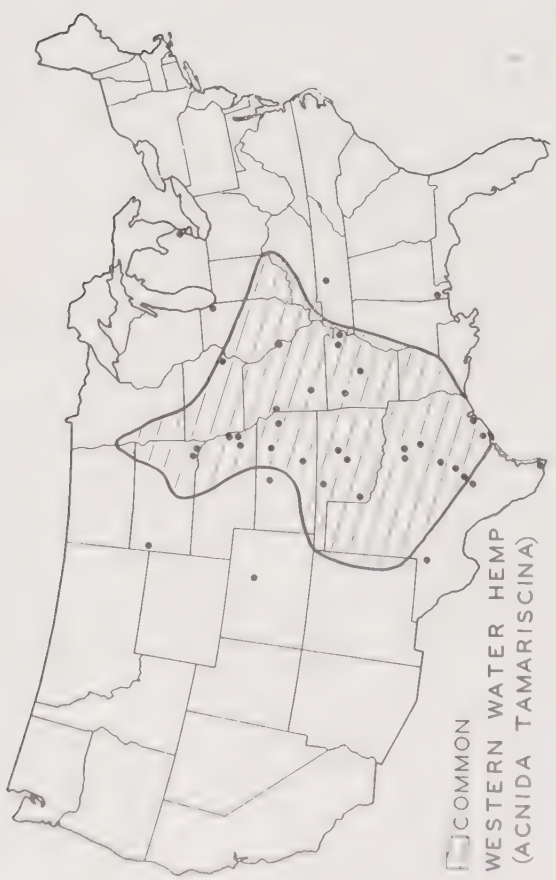


FIG. 191. See legend on page 545.



FIG. 195. Maple Flower (top), key or fruit (center), leaves (bottom). This tree is predominantly entomophilous.

elm, maple and birch leaves, reacting to maple. Desensitization relieved his asthma. He did not react to maple pollen.

Box elder. *Acer negundo* L.—This, the ash-leaved maple, replaces the above species in the West and is a plant of distinct importance from Missouri to Utah, Colorado and southern Texas. The fruit of all species of maple is the characteristic so-called key consisting of two-winged seeds, only one of which usually develops. Figs. 193, 195, 196.



Fig. 196.—Box Elder Blossoms, West Liberty, Iowa. (Courtesy of Dr. C. L. Fenton.)

The Linden Family. *Tiliaceae*

Linden, *Tilia americana* L., is insect pollinated and appears not to be a factor in pollinosis although enough of the pollen grains are carried on the wind to be deposited at times on pollen plates.

The Olive Family. *Oleaceae**

Ash. *Fraxinus americana* L.—While this tree is widely distributed, almost throughout the United States and Canada, and sheds large quantities of wind-borne pollen in April and May, it has not been found to be of material importance in pollinosis. Figs. 201, 202.

Privet. *Ligustrum vulgare* L.—Four members of the Ligustrum family, privet, lilac, syringa and forsythia, are so widely used in gardens that they may well be responsible for sporadic attacks. Privet has come under suspicion more frequently than the others. The writer has observed positive skin reactions in patients who themselves had suspected privet but has not found it necessary to desensitize. Dunbar states that Ligustrum is responsible for much pollinosis in China.

Privet pollen has three, rarely four, germinal folds and a deeply, coarsely reticulated exine. Pollination is in June. Fig. 198.

Ligustrum is abundant throughout the southeastern states where it is widely cultivated and trimmed as hedges. Ligustrum vulgaris grows as far north as New England but is less abundant in the North. Evergreen or Japanese privet grows as far north as Philadelphia. Thiberge (1934) found this an important hay fever plant in New Orleans in 3 of 56 local

*Hay fever due to olive pollen has been reported in California.

hay fever patients. Skin reaction was stronger to this than to any other pollen extract. Untrimmed, the bush grows to a height of 10 or 15 feet. Thiberge recommends repeated trimming as is done in hedges to diminish the quantity of bloom.

The Plantain Family. *Plantaginaceae*

There are a number of members of this family, three genera and over 225 species, but English plantain is the only member which has been shown to be of significance in pollinosis. This is well distributed over the United States and southern Canada and known to all who have lawns, as the weed which accompanies and follows dandelion. It has a similar circular basal distribution of long leaves from the center of which naked grass-like stems or scapes extend upwards six inches or more, terminating in a spike or head superficially re-



Fig. 197.—Ash. Detail of leaves.

sembling the head of timothy, but shorter and fuller. The broad leaf plantain which is as common has not been found to be of importance.

English plantain. Narrow leaf plantain. *Plantago lanceolata* L.—This plant invades lawns more frequently than the others. It flowers in May, June and July, and is a secondary or minor cause of hay fever, occasionally a primary cause in individual patients.

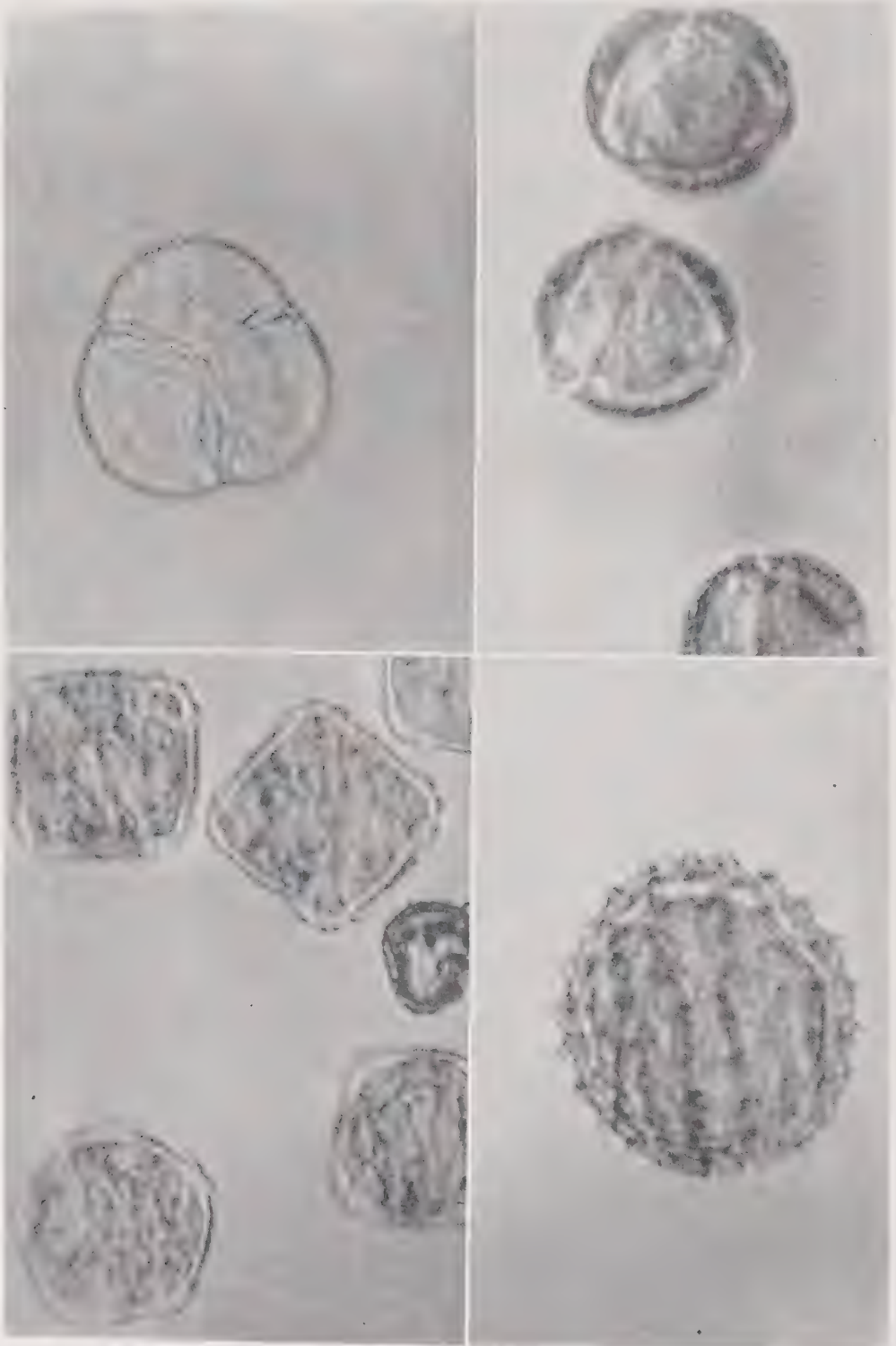


Fig. 198.—Pollens. Upper left, rhododendron (in vaseline); upper right, privet (in saline); lower left, white ash (in saline); lower right, dandelion (in oil).

Pollen grains are spheroidal, without germinal furrows but with from 7 to 14 pores varying somewhat in size and shape but usually circular. Exine is thin, rather granular. When dried the grains are shriveled. Pores are fairly evenly distributed. Exine is slightly



Fig. 199.—English plantain.

thickened around the germinal pores, especially the larger ones, giving a slight crater-like or umbilicated appearance. According to Wodehouse the pollen grains vary surprisingly in size. The pores do likewise, although they are quite constant in size on each individual grain. In general, larger grains tend to have larger pores, and a greater number of them.

This weed is anemophilous, shedding pollen over rather a long period, from April to November, most abundantly from May to August. The grains are usually abundant on pollen slides.

See Figs. 194, 199.

Bernton (1925) found 4.3 per cent of hay fever patients allergic to English plantain; 16.6 per cent of spring hay fever cases reacted. Blumstein and Tuft (1937) found 20 per cent of their spring hay fever cases and 7.7 per cent of



Fig. 200.—Goldenrod.

all hay fever cases regardless of season reactive to plantain. By passive transfer experiments with neutralization and crossed testing they established that the pollens of English and common or broad-leaf plantain are identical and bear no relationship to those of timothy and ragweed. They found the ophthalmic test valuable in differentiating the relative importance of grass and English plantain.

The Composite Family. *Compositae*

This is the largest of all of the plant families including from 11,000 to 12,000 species. Its members represent the highest evolutionary development. The outstanding differentiating characteristic is that the flowers are not single but each flower as we usually think of the term is a composite aggregation of a large number of individual flowers.



Fig. 201. Prairie sage (*Artemisia ludoviciana*).

The family of composites is divided into a number of genera, chicory, ragweed, thistle, etc. Some botanists class the first two as separate families, limiting the composites to the thistle family. The thistle family is still further divided into the aster genus, which contains goldenrod, chrysanthemum, aster, the sunflower genus; and others

The writer accepts Wodehouse's classification not only because his monograph on pollen grains has been drawn on abundantly in this discussion but also because, as Wodehouse points out, such a classification provides a more readily comprehensible picture of the evolutionary development of the pollens in these groups.

This evolutionary development from entomophily to anemophily may be readily followed in those representative pollens of the group with which allergists must become familiar. Such representatives are dandelion for the chicory tribe, goldenrod for the aster tribe, artemisia for the mayweed tribe, and finally the ragweed tribe.



Fig. 202.—Sagebrush. Variety photographed in Arizona.

The Chicory Genus. *Cichorieae*

Members of this group are characterized by heavy sculpturing of the exine, made by the heaping of exine material into vertical ridges surrounding the three germinal pores which are connected with each other by intricate systems of similar interlacing ridges giving remarkable and beautiful geometric patterns to the entire grain. These anastomosing ridges enclose depressions devoid of spines, smooth floors of extremely thin exine. The picture might be duplicated to some extent by a series of three or four coxcombs placed variously, with their ends touching and inserted vertically in an old-fashioned kaleidoscope. As the kaleidoscope is turned many different patterns are formed and this is the impression given by a collection of different pollens of the chicory genus.

Dandelion. *Taraxacum officinale* Weber. This pollen is a typical example. The grains vary considerably, about half being asymmetrical or otherwise abnormal. The vertical crests are not easily recognized in unstained specimens. Dandelion is a small herb most widely distributed through the United States, Europe, and elsewhere. It is insect-pollinated but responsible for some sporadic pollinosis. Positive dandelion reactions are usually associated with positive ragweed reactions, but the writer has observed cases of dandelion hay fever occurring in the spring time which were not relieved by perennial ragweed treatment or by coseasonal ragweed treatment during the dandelion season, but which were adequately relieved by injections of dandelion pollen extract. If, therefore, a ragweed allergic experiences symptoms during the earlier dandelion season, which are not otherwise explained, and if there is a reasonably close exposure, testing and treatment with this pollen may give relief.

See Figs. 198, 206.



Fig. 203.—Coast sage.

The Aster Genus. *Astereae*

In this group which is still chiefly insect pollinated, vertical ridges no longer appear in the pollen, but in their place we find well-developed conical spines of uniform size and apparently uniformly distributed over the surface.

Like members of the chicory group, the pollens in the aster genus vary considerably in size, shape and the number of spines. Differentiation of the species by the appearance of the pollen is unsatisfactory.

Goldenrod. *Solidago* L.—This pollen grain usually has three germinal furrows, sometimes four or even six. Spines are short-conical, sharp pointed, rather granular at the base, but smooth and homogeneous at the tip.

Goldenrod is so widely distributed through nearly all states of the Union that it was once suggested as our national flower. There are several species, most of which shed little pollen, but at least two produce abundantly. While goldenrod causes only sporadic pollinosis, the pollen at times becomes atmospheric and may be found upon slides. Vaughan and Crockett have described cases allergic to goldenrod and ragweed that were not adequately relieved until goldenrod extract was added to the treatment material. They found that approximately one-third of ragweed positive persons also react positively to goldenrod. Wodehouse states that under normal weather conditions, during the season, goldenrod pollen averages about 1 to 2 per cent of the total pollen caught on slides. In dry windy weather the percentage rises considerably. This is especially true toward the end of the ragweed season when goldenrod as a rule is still pollinating abundantly. At that time goldenrod pollen may even outnumber ragweed pollen on the slides. Fig. 200.



Fig. 204.—Pigweed (*Amaranthus hybridus*).

The Mayweed Genus. *Anthemideae*

In this group the exine is distinctly coarse-granular and the spines are broad, conical and sharp pointed, large in proportion to the size of the grain. The shorter the spines, as a rule, the more closely together they are placed.

Some members of this group are insect-pollinated, while others are wind-pollinated. As has been brought out, the development of wind pollination

is accompanied by loss of sculpturing and thinning of the exine. This is seen especially well in members of the mayweed genus where insect-pollinated grains possess well-developed spines and thick exine while those which are wind-pollinated have but vestigial spines and a much thinner exine. The



Fig. 205.—Mugwort.

spines may even be absent. We see first the loss of sculpturing which was present in the elcory genus, with replacement by spines, which in turn are replaced by vestigial spines or none at all. In rayweed, which is wind-pollinated, the spines are very short, nearly vestigial, while in the atten[sic]as there are no longer

any spines at all. With this loss of surface decoration there is a loss of the lipoid substance or surface oil which causes the grains to stick together and prevents them from being carried on the air.

Daisy and chrysanthemum are familiar examples of insect members while the artemisias are wind borne and are of more than sporadic allergenic significance.

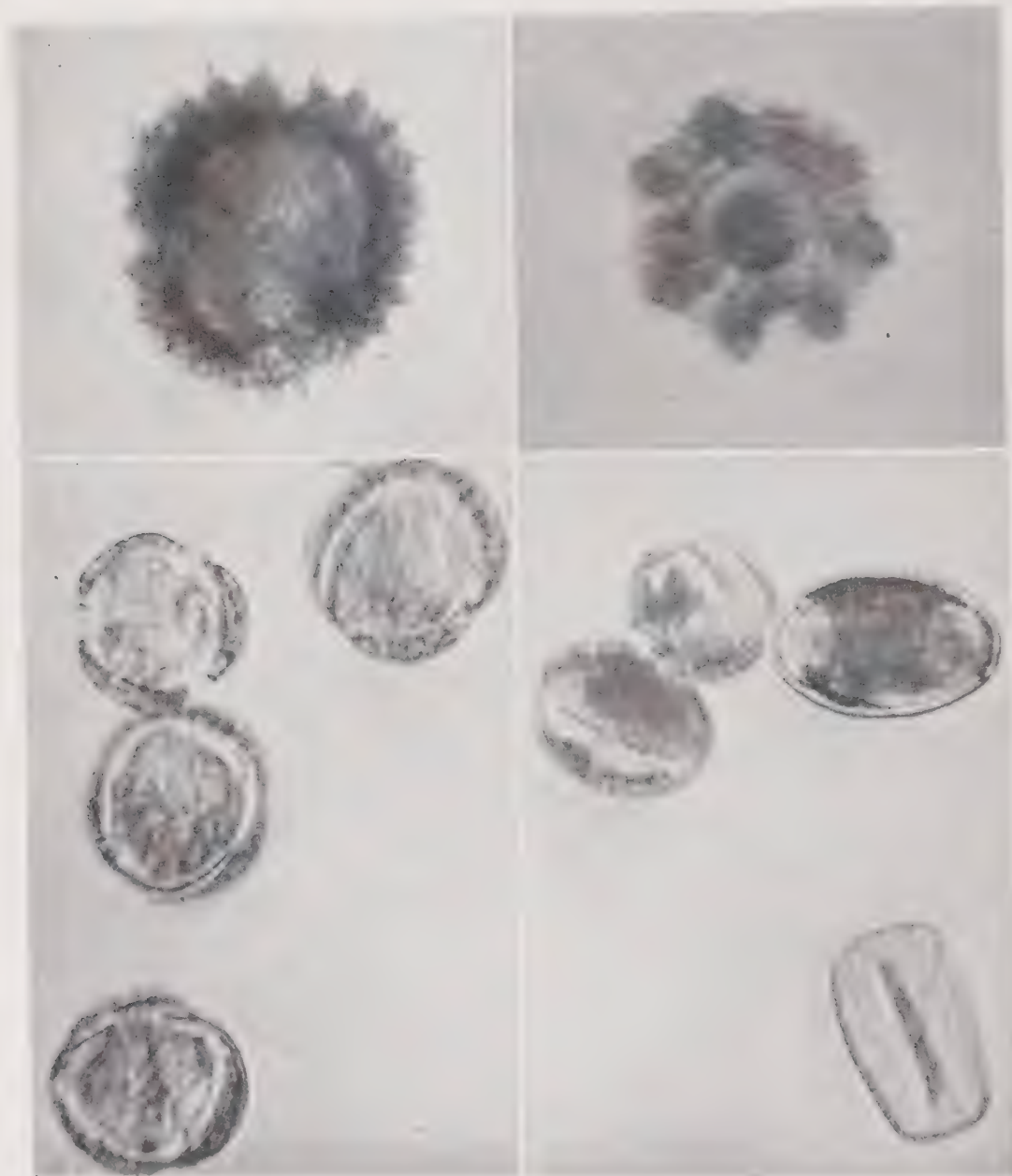


Fig. 206.—Pollens. Upper left, dandelion (in saline); upper right, dandelion (methyl green); lower left, biennial sage (in saline); lower right, biennial sage (in oil). Dandelion focus is on the equator (upper left) and on the surface (upper right), to show the depth and modeling of exine into ridges and valleys.

Sagebrush. Mugwort. Wormwood. *Artemisia L.*—In all members of this group the spines are extremely minute, vestigial, and in a few cannot be recognized at all. All members are wind-pollinated, flowering in general from the end of July to October.

The wormwoods or artemisias require much less moisture than the ragweeds. Partly for this reason, they assume an importance in the West comparable to that of ragweed, east

of the Rocky Mountains. They are especially important in the western mountain region and along the Pacific Coast, where they constitute one of the chief groups of pollen offenders. There are several important species. Figs. 194, 201, 202.

Sagebrush. *Artemisia tridentata* Nutt., is of greatest importance, covering as it does thousands of square miles of semiarid mountainous regions. Were the territory more densely populated it would be an even more important weed. It is especially abundant in Montana, Utah, Wyoming, Colorado and Nevada, where it grows as a shrub or small tree, covering the mountain sides with grayish green foliage. Fig. 215.



Fig. 207.—Short ragweed.

Common mugwort. *Artemisia vulgaris* L.—This is abundant especially in the valleys of California where it causes considerable pollinosis. It is also known as prairie sage, hoary sage and white leaved sage. Other varieties which are of some importance especially in the West are annual wormwood (*Artemisia annua*), coast sage brush (*Artemisia californica*), biennial wormwood (*Artemisia biennis* Willd.), carpet sage (*Artemisia frigida* Willd.), Indian sage tonic (*Artemisia dracunculoides* Pursh), dwarf sagebrush (*Artemisia Biachora* A. Gray).

See Figs. 203, 204, 205, 206, 211.

The Ragweed Genus. *Ambrosia*

Members of this genus possess pollen which usually has three germinal furrows, occasionally four or six, which may be long or short. The exine is slightly thickened but not as much as in entomophilous members of the fam-

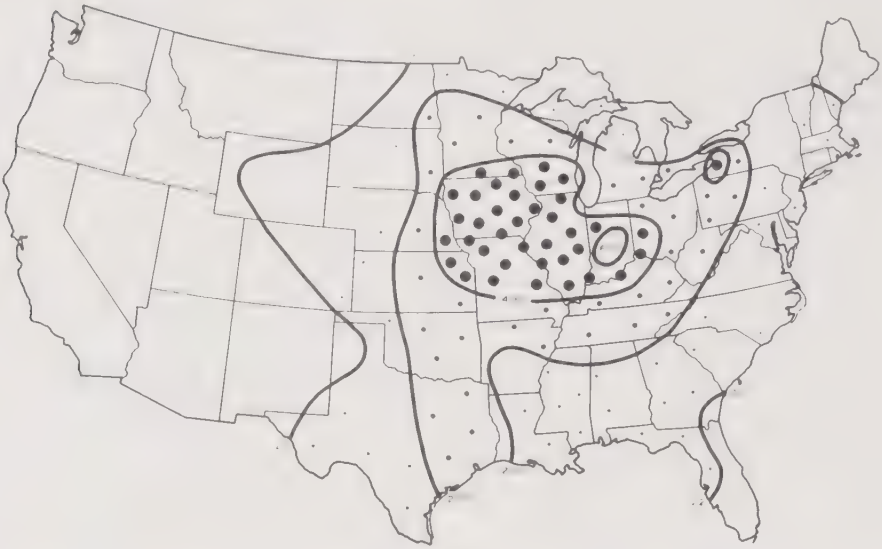


Fig. 208.—Ragweed isopolls. Zones of atmospheric ragweed density in the United States expressed in pounds of pollen per square mile, based on Durham's calculations.



Fig. 209.—Giant ragweed showing detail of leaves. Leaves may also be five lobed.

ily. It is granular and in most instances provided with short spines which may be pointed, rounded or vestigial. Wodehouse believes that the ragweed genus is more closely related to certain others of the compositae, especially the sunflower group and the mayweed genus, than are many of the other compositae to each other. There is also a close relationship between ragweed and the artemisias just described.

In the ragweed genus as in asters and mayweeds one may observe the evolution of the pollen grains from the thick walled exine toward the smooth thin wall such as that of cocklebur.

Nearly all species of this genus have small pollen although cocklebur is an exception.



Fig. 210.—Unusually tall giant ragweed collected near Memphis. (Courtesy of Dr. John P. Henry.)

Short ragweed. Dwarf ragweed. *Ambrosia elatior* L.—Here the pollen is characteristic of the group, with three germinal furrows, rarely four, and distinctly flattened spines which tend to be pointed at their tips. Exine is thin, granular. When caught in oil or vaseline the furrows are, as a rule, easily seen.

This is the chief cause of late summer and fall hay fever in the eastern half of the United States. Flowering occurs from about the middle of August to about the middle of October. It commences earlier in the North than in the South, the difference in time amounting to as much as two weeks or more.

Common ragweed, which in the earliest writings on pollinosis was termed Roman worm wood, grows by preference along the roadside, in vacant lots and in tilled soil from which the crop has been cut. In the United States it grows most profusely in the Mississippi drainage area including the tributaries, the Ohio drainage area and the lower reaches

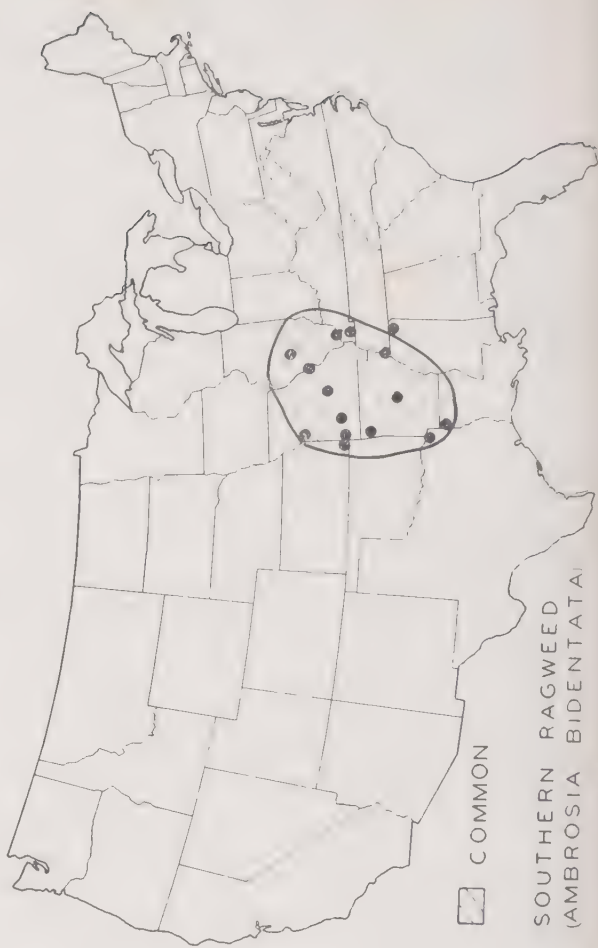
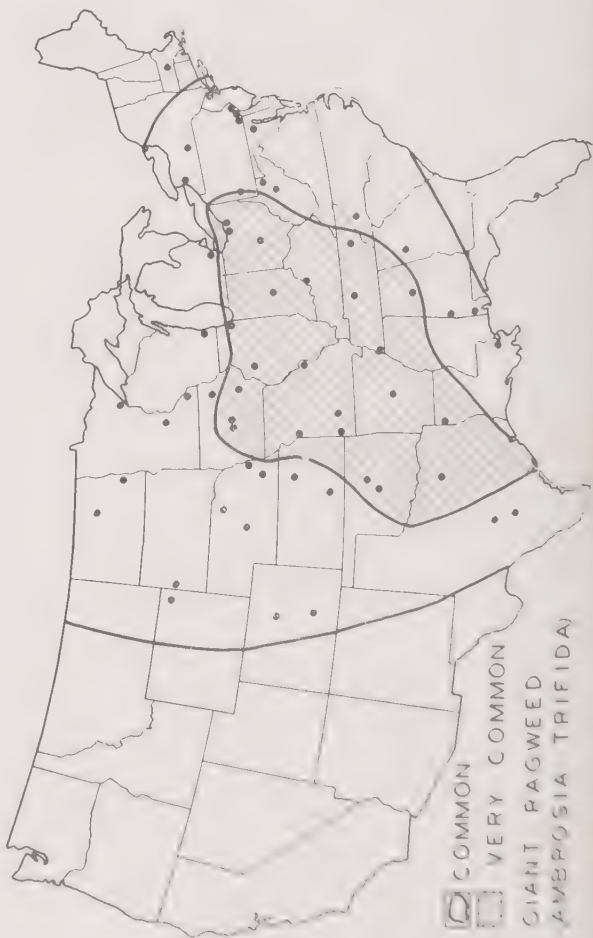
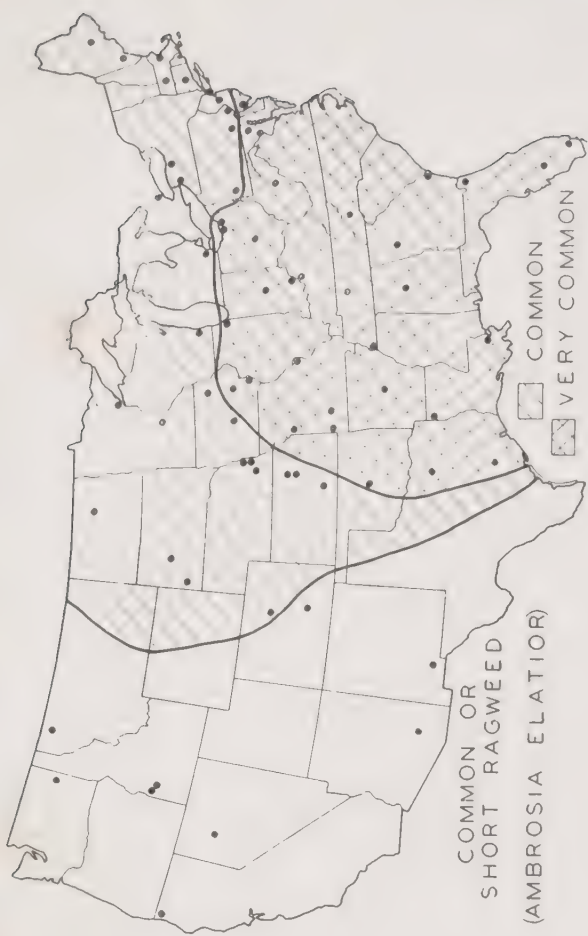


Fig. 211. See legend on page 515.

of the Missouri. The pollen is most abundant in the region from Toronto and Buffalo, west of the Alleghenies, spreading across southern Michigan, Ohio, Indiana and Illinois, and on into Iowa, Missouri, Kansas and the eastern half of Oklahoma. East of the Appalachian Highlands it is still the chief factor but the atmospheric concentration is far lower than in the areas described. The western limits are approximately San Antonio, Oklahoma City, Denver

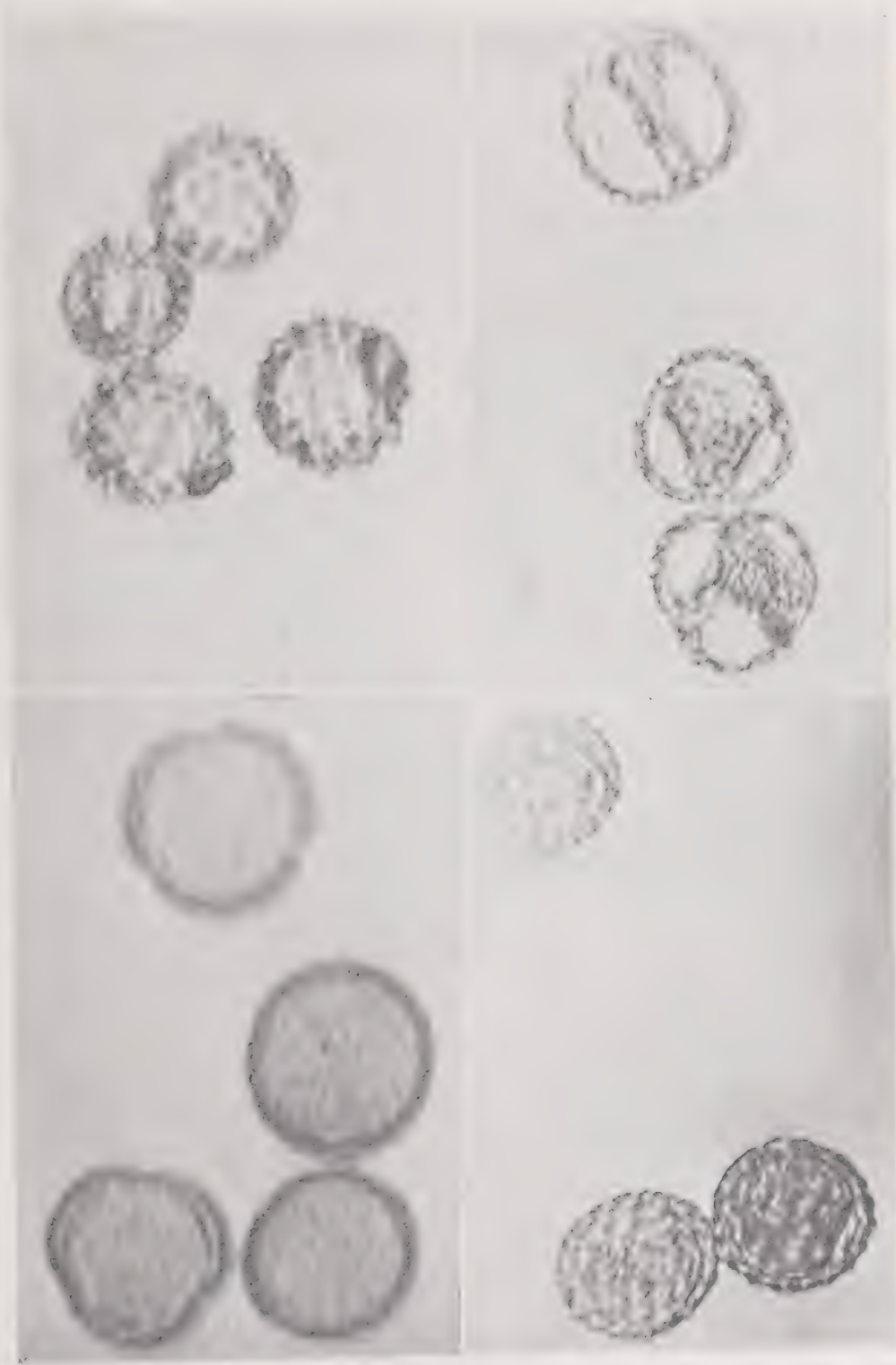


Fig. 212.—Pollens. Upper left, giant ragweed (in saline); upper right, short ragweed (in oil); lower left, rabbit bush (methyl green); lower right, marsh elder (in oil). Note that exine is less spiculated than in dandelion or sunflower.

and Billings, Montana. The northern reaches include Winnipeg, the northern shores of Lake Superior and southern Ontario, to Quebec and on through Maine and New Brunswick. To the south it extends to the Gulf of Mexico. Figs. 207, 208, 211, 212.

Giant ragweed. *Ambrosia trifida* L.—The pollen is not readily distinguishable from that of common ragweed. It is somewhat smaller and its spines are rather larger, more pointed and less closely arranged.

This plant has the same general distribution as short ragweed, with minor variations. The extreme western distribution is roughly the same but in Texas it grows farther west and farther south, to the Mexican border. Like short ragweed it extends northward to Winnipeg, but is not found in Canada east of Lake Superior nor is it sufficiently abundant in the New England states, Florida and the southern part of Georgia to be of allergenic importance.

The plant is much larger than its companion. While short ragweed may be three feet high, giant ragweed often reaches a height of thirteen feet. It grows abundantly along river bottoms, less so on uplands, and sheds pollen much more abundantly than does short ragweed. However, because of its much sparser distribution, it contributes less total pollen. The flowering period is the same in both. Figs. 209, 210, 211, 212.



Fig. 213.—Western ragweed.

Southern ragweed. *Ambrosia bidentata* L.—Pollen grains resemble those of giant ragweed. This plant resembles short ragweed in size but differs chiefly in the appearance of the leaf. Short ragweed leaves are open, feathery, fern-like, while those of southern ragweed are lance-shape, the upper ones slender, the lower broader and bi-lobed, the latter character giving origin to the botanical name. Southern ragweed is not, as its name might imply, the ragweed of importance through the South. It grows in southern Illinois, Missouri and Arkansas and in portions of contiguous states, where it is an allergen of secondary importance. The blooming period is from July to September, especially in August and September. See Fig. 211.

Western ragweed. *Ambrosia coronopifolia* T. & G.—The pollen is scarcely distinguishable from that of giant ragweed. This plant differs from its eastern cousin in that it is a perennial, propagating by creeping rootstocks. It is similar in appearance to short ragweed although the leaves are thicker, firmer. The leaves are not as abundant on the plant.

It grows through the western half of the United States, including the Dakotas and Nebraska, the western half of Kansas, Oklahoma and Texas, and the northern half of Mexico. It extends into Canada to about the level of Winnipeg and crosses the mountains into California but is not found west of the Cascade Mountains, along the coastal regions of Wash-

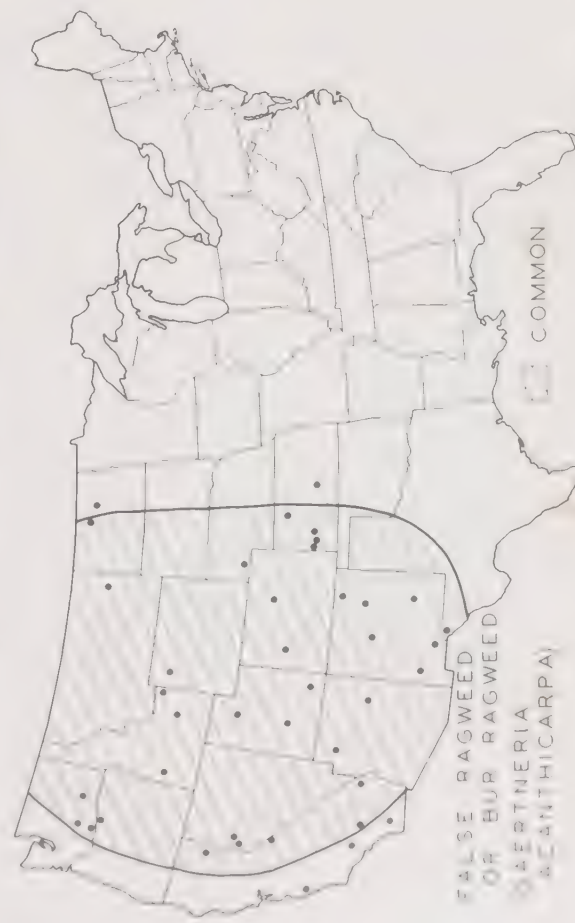
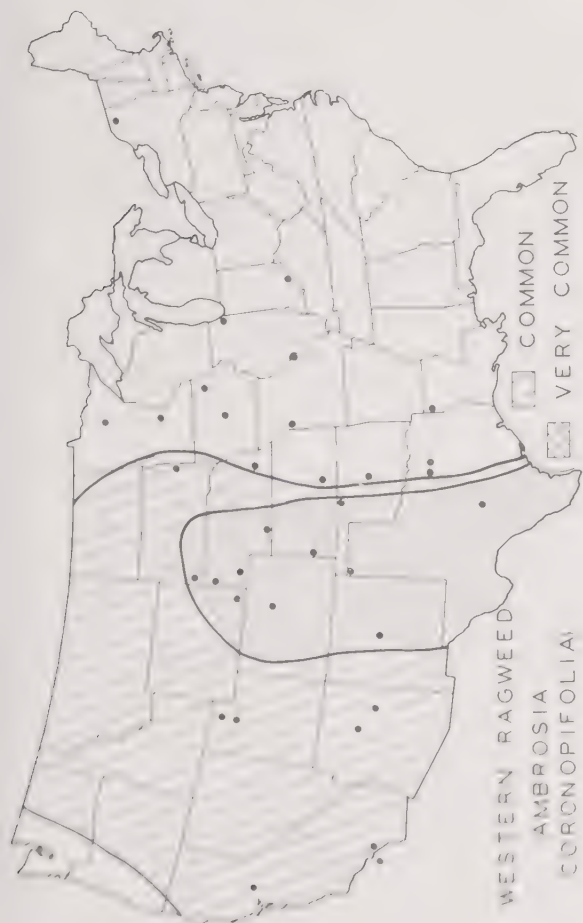
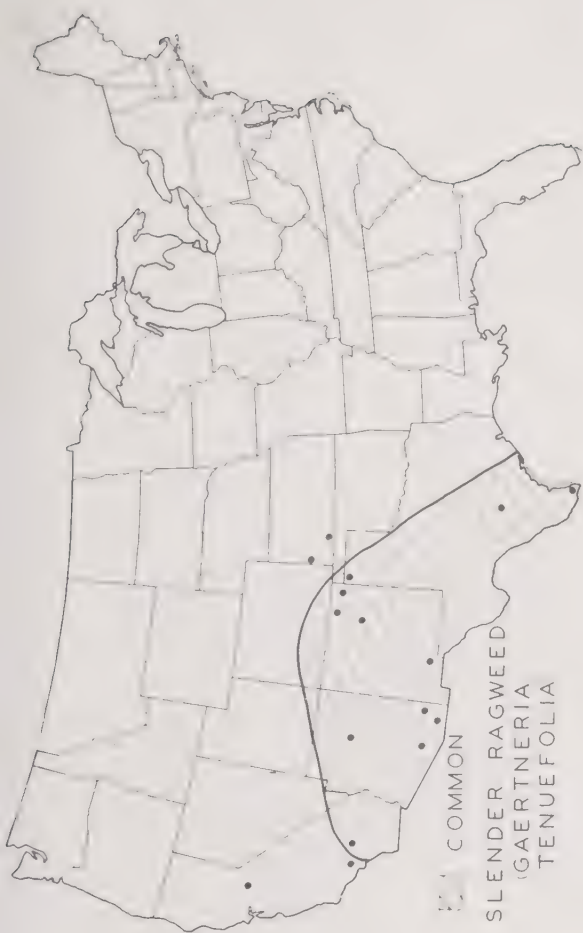


Fig. 216.—See legend on page 315.

ington and Oregon. It is of chief significance in southern California and Texas, decidedly less so in the regions farther north. The flowering period is long, from the end of July to October. Figs. 213, 214.

False ragweeds. *Franseria*. *Gutierrezia*. The false ragweeds resemble short ragweed, are found chiefly in the plateau states, and constitute a secondary factor in pollinosis. There



Fig. 215.—Rabbit bush (*Franseria deltoidea*) and sagebrush near Taos

are three of special significance: (1) *Franseria tenuifolia* Harv. and Gray (slender ragweed), a perennial which flowers from May to November and is responsible for considerable pollinosis in Arizona and California; (2) *Franseria acanthocarpa* (Hook.) Condit, false ragweed, also called big ragweed, which is of some significance in the western mountain range.

and (3) *Franseria deltoidea* Torr., the rabbit bush of Arizona and New Mexico. While *acanthicarpa* is an annual or biennial, growing from seed and therefore does not flower until August, *deltoidea* is a perennial, growing from rhizomes and consequently flowers much earlier, in the spring and early summer. See Figs. 212, 214, 215.

The false ragweeds are found in approximately the same distribution as western ragweed.

Marsh elder. *Iva*.—The *Ivas* constitute a member of the ambrosia genus or family. Pollens are similar to those of the ragweeds, the spines, however, being less prominent than those of short ragweed. Germinal furrows are very short. Exine is granular. Pollination occurs in July and August. Figs. 212, 218.

Burweed marsh elder.—According to Durham this plant is no longer considered an *Iva*, but is classified as *Cyclachaena xanthifolia* rather than *Iva xanthifolia*. The pollen grains have long, tapering germinal furrows and prominent spines.



Fig. 216.—Cocklebur.

Cocklebur. *Xanthium* L.—This, the last important member of the ragweed genus as far as pollinosis is concerned, is found in nearly every part of the United States. It grows best on land that has been cultivated.

Its pollen is not abundant. The grain is large, exine is thin, and spines are roughly similar to those of giant ragweed. Exine is conspicuously granular. The two species considered of some importance in pollinosis are common cocklebur, *Xanthium saccharatum* x. c

Britton, which blooms from the end of July until October, and spiny clotbur, *Xanthium spinosum* x. s. L., which is of some importance in California where it blooms from June to November. Figs. 216, 217, 218.

Pyrethrum, *Chrysanthemum coccineum* Willd., closely related to chrysanthemum, belongs in the large group of plants of which ragweed is a member. Feinberg (1934) observed

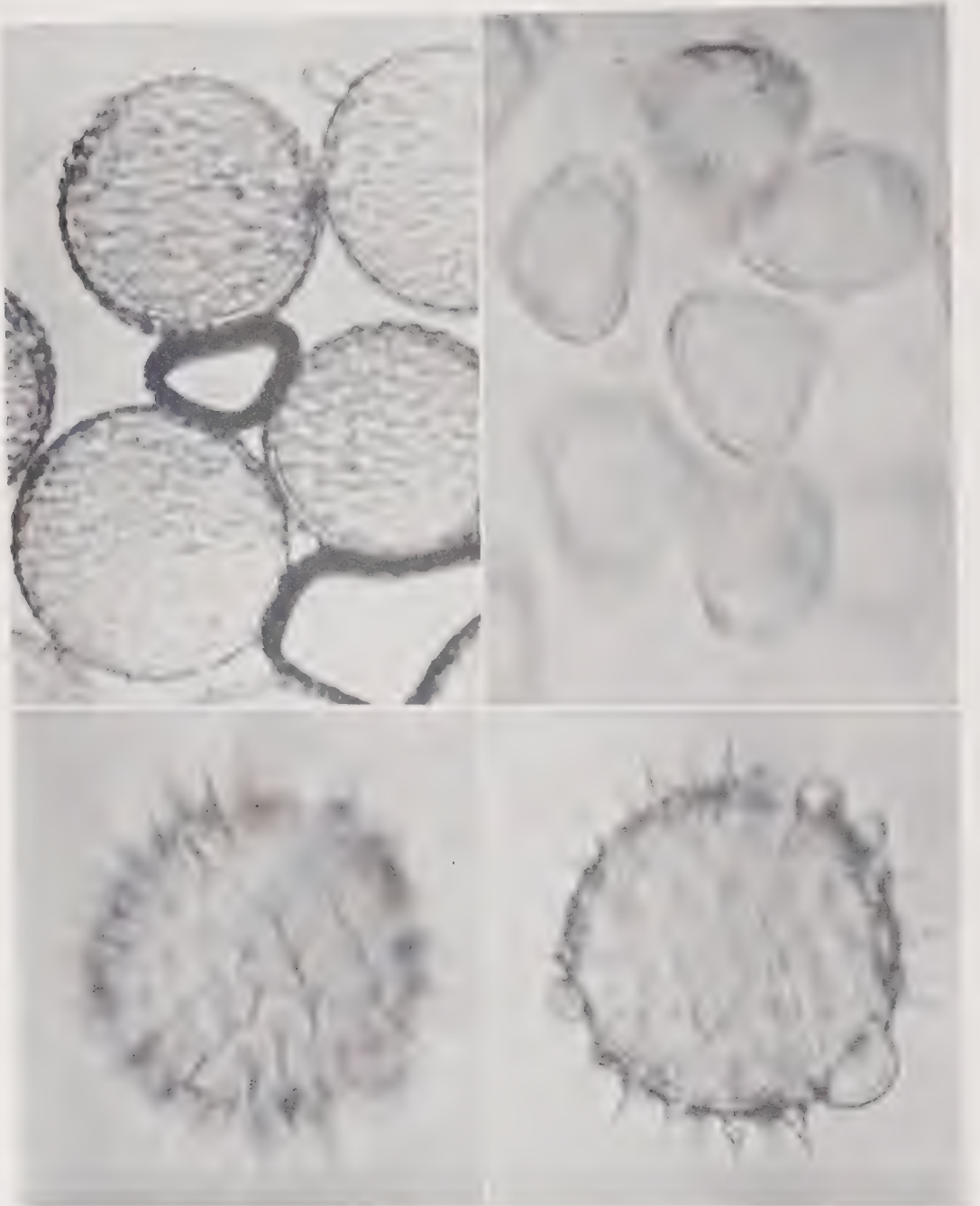
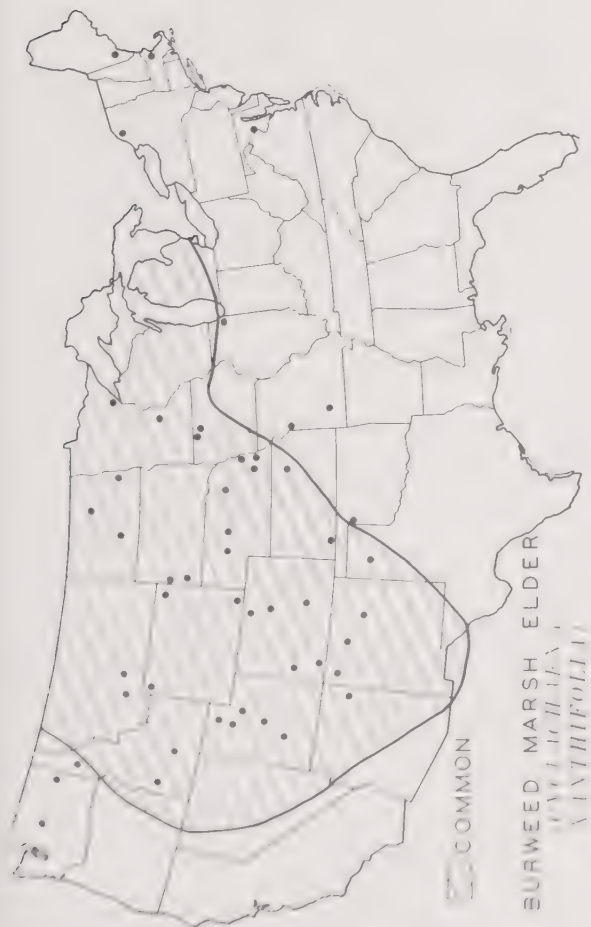
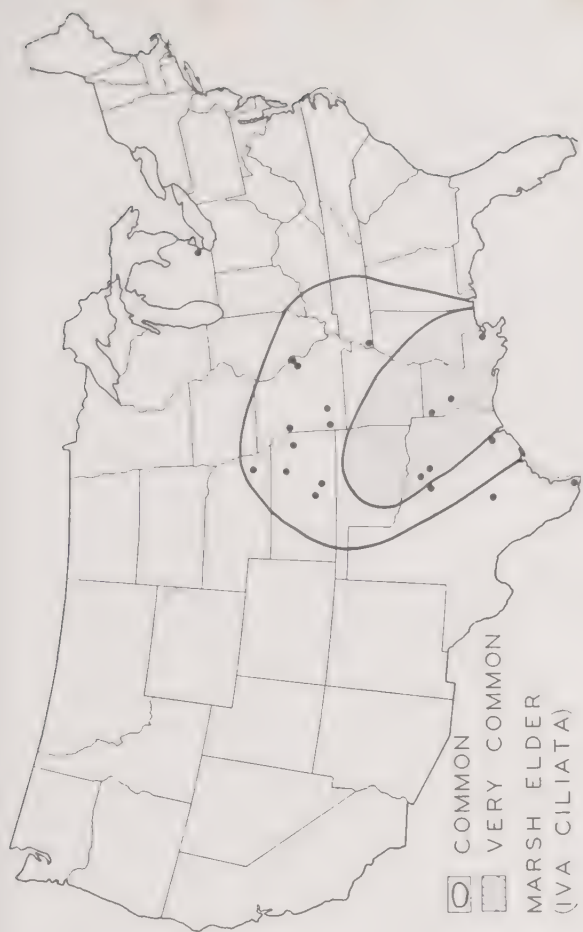


Fig. 217.—Pollens. Top left, cocklebur (in saline); top right, eucalyptus (methyl green); lower left, sunflower (in saline); lower right, sunflower (in saline). Sunflower focus is at the surface (left) and the equator (right) to show pronounced spiculation.

that in 225 cases reactive to ragweed, 42.6 reacted also to pyrethrum. In a control series with asthma and hyperesthetic rhinitis, not due to ragweed, less than 1 per cent reacted to pyrethrum. This suggests group sensitization involving pyrethrum and ragweed. Serum of a patient reactive to ragweed and pyrethrum, transferred to normal skin, could be desensitized with pyrethrum, after which ragweed extract failed to cause positive reaction.



This would indicate the presence of a similar or identical antigen in both. Feinberg brings out the point that a person sensitized to ragweed might have trouble at other times in the year, from pyrethrum. Occasionally horticulturalists have inhalant allergy from the plant pollen, but the more frequent source of trouble is the powdered petals, used in insect powders and sprays.



Fig. 219.—Spanish needle (*Bidens bipinnata*), responsible for one case of hay fever in the writer's experience.

Miscellaneous

Piqueria spp. Langley has reported hay fever due to piqueria pollen. *Piqueria trinervia* is used as a spray with cut flowers, chiefly from November to January. As a consequence it is introduced into many homes. Among 52 patients I gave positive reactions. All who reacted to piqueria also reacted to ragweed. The reverse was not true.

Catalpa spp.—Swineford has observed an asthmatic whose symptoms are due to catalpa pollen. This is entomophilous and exposure must be fairly close, such as, in Swineford's case,* walking down an avenue of catalpas.

*Swineford, Oscar, Charlottesville, Va. Personal communication.

CHAPTER XLVII

ETIOLOGIC DIAGNOSIS IN POLLINOSIS

Differential diagnosis.—The general principles of diagnosis have been discussed in Part IV. Occasionally, there may be uncertainty whether one is dealing with pollinosis. Hay fever is often mistaken for an acute head cold and vice versa. The latter, however, customarily displays a regular sequence with early profuse watery secretion, followed later by a thick, yellowish semipurulent or purulent discharge. Examination of the nasal secretion for eosinophiles and neutrophiles aids materially. The symptoms of pollinosis may be confined to the ocular conjunctiva, the nose, or the lower respiratory tract or may at times involve two or more of these localities.

A history of seasonal recurrences coincident with the pollinating period of certain plants aids in distinguishing pollinosis from other respiratory allergic reactions.

In the writer's experience it is unusual to observe pure uncomplicated pollinosis without evidence of some other allergic sensitization. A pollen allergic may at the same time be sensitized to a perennial inhalant allergen such as dust, orris root, feathers, pyrethrum, silk, etc.; he is very often allergic to food; and still more frequently gives positive reactions to foods which, however, have not been found to cause symptoms. This fact is of some importance since the writer has observed that although the majority of cases of pollinosis respond to pollen therapy alone, it is sometimes necessary, in addition to control the other sensitizations before adequate results are achieved.

Interaction of allergenic excitants. Vaughan (1927) reported this type of condition in hay fever. Two of the original cases illustrate the present point especially well. The first, a woman with typical ragweed pollinosis of five years' duration and a history of intermittent attacks of urticaria of fifteen years' duration, had had four years of preseasonal desensitization without relief. She was first seen during the fifth season, after having received preseasonal desensitization. We found her reactive to the pollens of ragweed, sunflower, daisy and rose and to egg, wheat, carrot and pepper. No attempt was made at further pollen desensitization. She was placed upon a diet—the avoidance of the four foods mentioned. This promptly relieved her hay fever. We may say that in this case the lessening of the alimentary allergenic overload enabled her to tolerate the inhalant allergenic load without symptoms. After the season she returned to general diet with no symptoms other than occasional attacks of urticaria.

A man had had ragweed hay fever and asthma for years. He was found allergic to ragweed, rabbit hair, dog hair, chicken feathers and nine foods. Coseasonal pollen desensitization relieved his hay fever but had no beneficial effect upon the asthma. However, with the avoidance of the other allergens mentioned his asthma was also relieved. Outside of the ragweed season, through the remainder of the year he had neither hay fever nor asthma in spite of the fact that he was in contact with all of the allergens mentioned, except ragweed, much of the time.

Eyer mann (1928) reported similar conclusions, with cases of pollinosis rendered comfortable merely by food restrictions. He described five cases of hay

fever and two of hay fever with asthma, with 80 per cent relief following food avoidance and the avoidance of inhalants other than pollen. In a more recent survey (1938) of patients with vasomotor rhinitis and food allergy he reached the following conclusions.

In Patients Clinically Sensitive to Foods:

1. Multiple skin and clinical sensitivity is the rule rather than the exception.
2. Skin sensitivity is not an unerring guide to clinical sensitivity.
3. Skin sensitivity to pollen and inhalants other than pollen is not a command to treat with hyposensitization injections.
4. The foods eaten most frequently are the ones most likely to induce allergic vasomotor rhinitis.
5. Frequently food and inhalant avoidance is sufficient to bring about a satisfactory therapeutic result in perennial vasomotor rhinitis.
6. In the instances of perennial vasomotor rhinitis, skin sensitive to pollen, avoidance of food and inhalants other than pollen usually brings about a satisfactory therapeutic result; but in some the condition will be transformed into annual vasomotor rhinitis (hay fever).
7. When bronchospasm complicates the allergic reaction in the nose, inhalants are more likely to be the dominant causative agents.
8. Before determining that pollen injections are imperative, one should critically consider the clinical influence of foods and inhalants other than pollen. Observation through a season of pollination not infrequently will show that such injections are unnecessary, when other allergic factors are properly controlled. A few cases of hay fever are comfortable merely by food restrictions; others merely by avoiding specific foods and inhalants other than pollen.
9. In many of these cases, it appears that the persistence and duration and, possibly, the initiation and intensity of symptoms depend upon the total allergic dose.

The Balanced Allergic State

Since these early observations, a number of investigators have reached similar conclusions. An explanation of the relief obtained, not by avoidance of, or desensitization against, the major excitant, but by removal of other predisposing factors, is to be found in the writer's theory of allergic equilibrium or the balanced allergic state (1924).

Briefly, the theory is as follows. A person may be sensitized to some allergen, such as food, with which he comes in frequent or even daily contact, and yet remain free from symptoms. Peshkin and Rost, and Rackemann found that about 10 per cent of children without symptoms of allergy, are allergic to one or another allergen. They are in a state of equilibrium, remaining symptom free. The tissues can handle a given quantum of the allergen without upsetting the allergic balance. An overdose will upset the equilibrium, with consequent precipitation of symptoms.

One may be allergic to two substances, maintaining balance while in contact with one, but developing symptoms on exposure to both. It may not be necessary to remove both to gain relief, the equilibrium being reestablished following the avoidance of one. One may tolerate a given allergenic exposure, but experience symptoms when one's resistance or tolerance is lowered by extraneous nonallergenic factors such as fatigue, emotional upsets, constipation, infection, endocrine disturbance, mechanical irritation and the like. When a combination of two or more factors has overthrown the allergic balance, the latter may at times be regained by control of one or more, without control of all. Thus, a patient with pollinosis and food allergy may occasionally be relieved of his pollinosis merely by treatment of the food allergy. It seems probable that the relief obtained at times following nonallergic treatment of hay fever such

as local rhinologic treatment, colonic irrigation, dilute hydrochloric acid, may be attributable to readjustment of some of these other factors, thereby re-establishing a balanced allergic state.

The state of allergic equilibrium is a hypothetical condition the existence of which is strongly suggested by clinical observation. The same phenomenon may be described in different terms. Thus Baldwin states that the intensity of the allergic stimulus together with the individual reactivity of the patient is of more importance than the kind of stimulus. When one or more stimuli to attacks have been removed without completely eradicating the sum total of stimuli, response to the remaining stimuli is often less severe. The elimination of one set of stimuli, whether they be atopic, infective, contact or physical, will result in less reactivity to the remaining stimuli.

While there is much clinical evidence of a summation of effect of excitants, experimental proof is difficult. The observations of Pratt (1938) are against summation effect. He sensitized guinea pigs to two different antigens, thereafter determining the dose of each required to produce moderate anaphylactic shock. When this dose of both antigens was given simultaneously to one pig, the degree of shock was not increased. On the contrary a double dose of either one caused an increased response.

On the other hand, there is strong indirect evidence. Bernstein (1935) demonstrated experimentally that in the presence of an underlying sensitization, a substance, not in itself capable of sensitizing, can induce sensitization and shock when properly administered. The substance which he used has since been shown to be capable of sensitizing but is a very feeble sensitizer in guinea pigs. An intravenous injection of burweed marsh elder extract given three weeks after the sensitizing doses caused no reaction. If, however, the guinea pigs were sensitized with horse serum, either before or at the same time with the pollen injections, intravenous injection of burweed marsh elder three weeks later did cause shock.

This type of observation justifies us for the present in advising patients that the avoidance of allergens to which they are sensitized will probably help prevent their developing additional sensitizations.

Schultz and Swift (1934) reached somewhat similar conclusions concerning reaction to bacteria. They found that the reactivity of rabbit to horse serum is greatly increased by antecedent sensitization with repeated small intracutaneous injections or larger intravenous injections of streptococci.

The overthrowing of the allergic equilibrium or balance is well illustrated in 3 cases described by Hansel. A man allergic to lemon and feathers but under control with avoidance sensitized himself to chocolate candy by overdosage. Thereafter quantities of all three which had previously been innocuous caused trouble. A man with migraine was allergic to wheat but tolerated it in small doses. The same dose following an emotional upset caused migraine. This situation persisted for some time thereafter. A woman receiving constant dosage in perennial pollen therapy had a severe emotional upset shortly after one of her injections. She then experienced a constitutional reaction and thereafter for some time the dose had to be much smaller.*

The following case illustrates the interaction between physical allergy and atopic allergy. A woman is allergic to strawberries and tomatoes. She usually eats them with impunity but if after eating them she goes out into sunlight for a time, she develops a rash on the arms and neck. Sunlight alone does not cause this.

*Hansel, French K., St. Louis, Mo. Personal communication.

The writer has had occasion to observe for a number of years, a man allergic to milk and susceptible to ivy poisoning. He is exposed in the same locality each summer. When milk is a constituent of his diet he develops ivy dermatitis but in the summers when he has been avoiding milk he has been free from dermatitis.

The following illustrates clearly summation effect. A young woman very highly allergic to ragweed had been built up for perennial desensitization and had received 3 injections of 0.5 cc. of 1/50 extract at weekly intervals. She was on dietary restrictions including the avoidance of pork, mustard and chocolate. Thirty minutes prior to the fourth weekly injection of the same dose she broke her diet, eating a "hot dog" pork sausage with mustard and some milk-chocolate candy. Ten minutes after receiving the injection her eyes became red, her nose stopped up and she commenced to sneeze. Wheals developed at the site of injection, later spreading over the entire body. Her nose, eyelids and lips, feet and ankles, fingers and hands, swelled with angioneurotic edema. Intense pruritus developed over the entire body. She developed severe asthma and had great difficulty getting her breath; 0.5 cc. of adrenalin gave some relief although the angioneurotic edema and itching persisted the following morning. After this experience she remained on her diet, continued with the same dose of ragweed extract, and later increased gradually to 1 cc. just prior to the season, with no return of systemic reaction.

Need for detailed allergic study.—It becomes obvious that the diagnostic study of pollinosis is not completed with skin testing with the pollens. This procedure is a short cut, often sufficient, but for best results each pollinosis case should be studied for evidence of other allergy, especially foods and perennial inhalants, and should have the customary comprehensive diagnostic study in search for nonallergic factors which may play a predisposing part. The more scientific procedure is to make all of these studies at the beginning, but if this is not practicable, if only pollen studies have been made and treatment has been given, the physician should remember that in the event of unsatisfactory results they can often be greatly improved by more thorough study and simultaneous treatment of indirect or predisposing factors.

I have described, above, cases relieved by dietary restrictions alone. Others, not relieved by preseasonal or coseasonal therapy, have avoided positively reacting foods even though they have never experienced symptoms from them outside of the pollen season, with consequent relief. When the pollen season is over the patient returns to a general diet. His attention having been called to these certain foods, he will not infrequently find that some do cause mild symptoms out of season.

Testing methods.—Observers differ in the choice of testing methods. The writer has found the scratch test with 2 per cent, 3 per cent or 5 per cent weight by volume extract in glycerosaline to be adequate. When doubt exists following this test it may be repeated, sometimes with more definite reactions. If endermal testing is to be applied, it must be done with an extract in saline, or alkaline extracting fluid (Coca) and must be made so dilute as to preclude the possibility of a constitutional reaction; 1:5,000 dilution, weight by volume, is usually considered safe. If two 1:50, or 2 per cent, scratches have been negative to a given pollen, a stronger solution may be used endermally, such as 1:1,000. This is twenty times more dilute and theoretically five times more reactive than the scratch.

Significance of positive reaction. A positive skin reaction indicates sensitization but not necessarily that the particular pollen is responsible for symptoms. In the writer's clinic all cases of pollinosis, no matter what the season of symptoms, are tested with tree, grass and weed pollens. It is the rule rather than the exception to observe positive reactions to pollens which are in the atmosphere at times when the patient is symptom free. This is especially the case with tree pollens, less so with those of the grasses and weeds.

The question arises, then, as to *which of the positively reacting pollens should be used in treatment*. The answer is, obviously, those which are atmospheric when the patient has symptoms. This rule should be precise, not approximate. The following case illustrates the error of approximation.

A young lady had had fall hay fever for several years, for which she had been given courses of ragweed desensitization, never with satisfactory results. Preliminary discussion brought out that her symptoms invariably commenced between the first and fifteenth of August. In Richmond, ragweed pollinosis never commences before the fifteenth, rarely before the eighteenth. Goldenrod starts pollinating before ragweed, continues through the ragweed season and shortly thereafter. Realizing that the coincidence of symptoms with ragweed pollinosis was not exact, we tested with other pollens, and found her allergic to goldenrod and sunflower. Preseasonal desensitization with these two pollens achieved one hundred per cent relief.

Should one test only with those pollens which are atmospheric when the patient has symptoms? Provided care is used in their selection this is an adequate minimal procedure. However, when the patient has come from a distance for study it is safer to test with a comprehensive series of pollens. I have stated that we often find positive reactions to pollens which are atmospheric when the patient has no symptoms. It is surprising how frequently the patient at some time later develops symptoms at another time of year which, on reference to the record, are found to be associated with sensitization to these other pollens. In such cases the patient need not return for repetition of the study since the necessary information is already available.

The tendency toward group reactions within a biologic family should be borne in mind and justifies testing with various associated species within a given family. The writer finds that from 30 to 50 per cent of those reacting to ragweed also react to goldenrod. Occasionally, ragweed hyposensitization does not give adequate relief but a combination of ragweed and goldenrod does. In 1937 we observed three ragweed cases who unexpectedly had symptoms in the late spring which were found due to sensitization to closely related dandelion. Relief was obtained following coseasonal dandelion treatment.

Is it sufficient when dealing with a grass allergic to test with but one grass as representative of these closely related species? There is a very definite tendency toward group sensitization among the grasses, but Grubb and Vaughan were unable to find in a study of 300 cases that any single grass pollen reacted positively in every grass case, as an adequate representative of the entire group. Each individual pollen cross reacted with others in approximately 65 per cent but none cross reacted 100 per cent. Indeed, we found that 17 per cent of grass allergies reacted to only one pollen. Unfortunately, it was not always the same pollen and the single species-specific sensitization was found to occur, in different cases, to every grass tested. We, therefore, must recognize (a) group-specificity and (b) species-specificity among the grasses. The grass which in our experience cross reacted most frequently with others was red top (84 per cent). However, this percentage is not sufficiently high to make red top a universal test extract for grasses. Approximately 2 per cent reacted to red top alone. Fifteen per cent reacted only to other single pollens. If, therefore, one does not test with all potential grass pollens one must anticipate missing up to 15 per cent of diagnostic reactions, those occurring in patients who are strictly species-specific in their sensitization.

Grubb and Vaughan reached analogous conclusions in their study of the composites and the chenopodiales, the chenopod-amaranth group. This even

applies to giant and short ragweed; 3.5 per cent reacted only to short, not to giant, and 2 per cent reacted only to giant. The remainder reacted positively to both.

Conjunctival and nasal contact tests. There is evidence that the mucous membrane reaction is more reliable as an indicator of actual symptoms than the skin reaction. Positive skin reactions often occur when the patient does not have symptoms from the pollen, but a positive mucous membrane reaction usually coincides with symptom activity during the season. If, therefore, several pollens react positively and one wishes to determine which are of more probable etiologic significance, one may do so with the conjunctival or ophthalmic test as well as with nasal contact studies. (See Chapter XXI.)

Occasionally a pollen which should be the offender as judged by coincidence of symptoms and atmospheric prevalence fails to give positive skin reactions either to scratch or endermal tests. Here again ophthalmic and nasal contact tests may respond.

Passive transfer.—In persons with dermatographia, in whom all tests are positive, passive transfer may be used. It is conceivable that under certain circumstances a person living at a distance and unable to report in person might require diagnostic pollen or other allergen tests. Passive transfer could be used under such circumstances. The following case illustrates the procedure:

A young woman had suffered from ragweed hay fever while living in the United States. She had also had dysmenorrhea prior to marriage which had been relieved in great measure by egg avoidance for one week prior to and through each period. Having moved to Puerto Rico where there is no ragweed, she was relieved of hay fever. However, she developed seasonal asthma which occurred only "during the *flamboyant* season." The tree in Puerto Rico known locally as *flamboyant* somewhat resembles mimosa, is apparently entomophilous, and widely used as an ornamental. There was a tree outside the patient's bedroom window, overhanging the entire house. The patient was tested with mimosa pollen as a possible close relative and found negative.

Her serum was then obtained and preserved in the ice box. She was directed, upon her return to Puerto Rico, to collect *flamboyant* pollen and to send it in for testing. Upon its arrival a subject was passively sensitized with her serum and tested with an extract of the pollen.

CHAPTER XLVIII

TREATMENT EXTRACTS AND DOSAGE NOMENCLATURE

In view of the discussion of the preceding chapter it need but be said here that treatment should be directed to the patient as a whole, due consideration being given to nonspecific, nonallergic factors as well as to allergic factors other than pollen sensitization, such as food allergy and sensitization to perennial inhalants. The present chapter will deal with methods of specific pollen desensitization. The same principles apply in both hay fever and asthma and in the writer's experience dosages need not be modified according to age. Children tolerate the same dosages as adults. Modification of dose depends, rather, upon the intensity of the sensitization.

General principles. -While there are many exceptions the following generalizations usually hold.

Simple uncomplicated hay fever without associated profuse rhinorrhea usually responds well to pollen therapy alone.

When, in addition to nasal obstruction, sneezing and lachrymation, there is a profuse watery nasal discharge requiring the patient to use many handkerchiefs each day, there may be associated food allergy. Best results should then be obtained by specific pollen desensitization together with food avoidance.

When the response is with asthma, foods and other inhalants must often be considered, for best results.

In cases allergic to more than one pollen, or to a pollen and some other allergen, one allergen may be responsible for the hay fever, another for the asthma. Treatment may relieve one of the two respiratory symptoms while failing to relieve the other. When this occurs, further search must be made for the etiologic agent of the unrelieved symptom.

Pollen Units and Dosage Standardization

There are at least four methods of recording the strength of pollen extract or dosage, all in more or less general use. Three are roughly interchangeable while the fourth is not. While this lack of uniformity in designating dosage units results in some confusion in the comparing of the reports of various investigators, it represents an unavoidable step in the evolution of allergic therapy. There are valid objections to each of the four systems and each has certain obvious advantages over the others. As a consequence neither the National Institute of Health of the Public Health Service which has supervision over commercial biologic laboratories nor the Council on Pharmacy and Chemistry of the American Medical Association has as yet designated a standard unit for allergen extracts.

The pollen unit of Noon. Noon, of England, the first to successfully treat pollinosis, also suggested the first dosage unit. This is the quantity of allergen in the extract of one-millionth gram of pollen. Noon designated one gram of dry grass pollen as containing 1 million pollen units. If one gram of pollen be extracted in 100 cc. of fluid to make a 1 per cent extract, the entire 100 cc. will contain 1,000,000 units. One cc. contains 10,000 units and 0.01 cc. contains 100 units. If this 1 per cent extract be diluted 100 times, then 0.01 cc. will con-

tain 1 unit. Since it is customary to treat with serial dilutions of a concentrated extract, beginning with the most dilute, it is obviously a simple matter to start treatment with 1 unit.

An advantage of the Noon unit system is that the reporting of dosage deals only with whole numbers rather than fractions, since it is rarely necessary to start treatment with less than 1 unit.

Weight by volume or percentage system.—The original extraction of pollen is customarily made in rather concentrated form, 1 per cent, 2 per cent, 3, 5 or 10 per cent. Dilutions are made in multiples of ten. Most allergists prefer 2 or 3 per cent for original extraction. A 2 per cent extract may be designated 1:50. Diluted 10 times it is designated 1:500; another 10 times, 1:5,000, etc. It will be seen from Table XXXVIII that 0.1 cc. of 1:5,000 extract contains 20 Noon units; 0.01 cc. contains 2 units. The writer has found that 98 per cent of pollinosis in the East may be started on an initial dose of 10 or 20 units. Therefore, in the majority of cases only 3 dilutions are necessary, 1:5,000, 1:500 and 1:50.

Objections to these systems. The objection has been properly raised that the weight-by-volume method which is the basis for both nomenclatures is not scientifically correct because one is weighing the entire pollen grain rather than the active substance and that the proportionate amount of active allergen per grain varies in different pollens and even in the same species at different times. One is weighing inert material along with active substance, the former comprising most of the weight, and the two are not always proportionate. A batch of pollen of feeble antigenic potency would be designated as having as many units per volume of active material as one of high potency. A preferable method would be determination of concentration of the active substance itself.

Interesting observations have been made concerning the question whether allergenic potency of dried pollen diminishes with age. If pollen is properly dried and maintained in this condition deterioration is very slow. There is evidence that the activity of pollen even when fresh varies from year to year. Wilmer and Cobe believe that variation in excitant concentration occurs annually, depending upon climatic conditions. It may vary even in the same season. For this reason they felt that controlled horticulture might produce a more constant allergen. They found hothouse-grown short ragweed more potent than specimens obtained from the field by commercial houses during the same year.

Feinberg and Steinberg studied the reactivity of patients to extracts of pollen gathered in 1926, 1927, 1928, 1930 and 1931. The 1928 pollen was less allergenic than that for 1926, 1930 or 1931; 1927 pollen was also feeble but not as feeble as that of 1928. The fact that the 1926 pollen was more strongly allergenic than that of 1927 or 1928 indicated that ageing after collection is not the essential factor. This is also indicated by the observation of Thommen who found ragweed pollen forty years old still strongly allergenic.

While the keeping quality of dried natural pollen appears to be good, that of pollen extract is decidedly variable and appears to depend principally upon the method of extraction. Glycerin extracts or, more properly, extracts made in solutions containing glycerin appear to possess best keeping qualities. Piness has reported glycerin extracts as retaining antigenic properties for ten years. Others, notably Peshkin, feel that they commence to lose potency after about six months. Extracts without glycerin such as those in Coca's fluid begin to deteriorate after about three months, sometimes sooner.

The total nitrogen unit. To obviate the disadvantage of the weight by volume method (Cooke (1915) proposed standardization by the determination of total nitrogen as an index of protein content rather than by total bulk content. He described his unit in terms of fractions of a milligram of total nitrogen. Here, one was presumably dealing with an indirect measure of protein which was in turn presumably the active allergen. However, as investigation proceeded, it was realized that pollens, like foods and epidermals, contain not a single protein but two or more, and that only one of these may be allergenic. Furthermore, it became evident that much of the total nitrogen represented nonprotein as well as protein nitrogen. Total nitrogen was therefore not an accurate measure of protein nitrogen or of protein. This same criticism is applied to the Clock method of standardization by complement fixation against antipollen serum, there being several proteins in pollen, only certain ones of which are allergenic.

The protein nitrogen unit of Cooke and Stull.—To avoid this difficulty Cooke and Stull next recommended the determination of protein nitrogen as a measure of protein content. Here again, all of the proteins, allergenic and nonallergenic, are included in the unit, but since nonprotein nitrogen, presumably nonallergenic, may represent as much as two-thirds of the total nitrogen, it becomes obvious that the determination of protein nitrogen is theoretically a nearer approach to accuracy.

In view of the fact that 0.00001 mg. is the smallest dose required even for the most highly allergic, this was selected as the protein unit. One hundred units would represent 0.001 mg. protein nitrogen. One-tenth mg. would represent 10,000 units. The scale of dosage lies between 1 unit and 100,000 units. The concentration of extract is expressed in units per cc. Extracts prepared from timothy, 3 grams per 100 cc., showed a total protein nitrogen content ranging from 0.05 mg. per cc. to 0.20 mg. per cc. Those from ragweed in the same concentration showed a range from 0.09 to 0.16 mg. per cc. The latter figure, 0.16 mg. per cc. would represent 16,000 units per cc.

Interchangeability of these systems.—The following table from Tuft shows the comparative values of the different units and makes possible the approximate translation of one to another. Here the total N is expressed in milligrams and the protein N is expressed in units and it is assumed that the protein N is approximately 40 per cent of the total N.

TABLE XXXVIII.—COMPARISON OF UNIT VALUES OF POLLEN EXTRACTS (TUFT)

WEIGHT PER VOLUME	MILLIGRAM TOTAL NITROGEN	PROTEIN N UNITS	NOON UNITS
1 c.c. of			
1-1,000,000	0.000016	0.64	1
1-100,000	0.00016	6.4	10
1-10,000	0.0016	64.0	100
1-1,000	0.016	640.0	1000
1-100	0.16	6400.0	10000

The active agent in pollen. For the past several years there has been considerable investigation to determine the allergenic substance in pollen and much questioning as to whether, after all, it is protein. Grove and Coca presented evidence that tryptic digestion did not destroy the antigenic activity and Black agreed with their conclusions. However, Stull, Cooke and Tennant, and Harsh and Huber contended that if proteolytic digestion were allowed to pro-

ceed far enough, the antigenic activity was lost. Caulfield, Cohen, and Eadie, and Stull, Cooke, and Chobot believed the antigenic substance is protein. Black then reported finding a polysaccharide which gave positive skin reactions and Caulfield reported satisfactory treatment with a carbohydrate fraction. Brown and Benotti believed the true antigen to be a carbohydrate combined with an alpha-amino group. Abramson, by electrophoretic and ultracentrifugal analyses, found in ragweed pollen "negatively charged major colorless components which are highly skin-reactive and which produce hay fever and asthma." The molecular weight was calculated to be about 5,000. The substance is believed to be "polypeptides of high molecular weight or proteinlike substances." Rockwell also found the antigen to be a polypeptide with a minimum molecular weight of 4,453, it is levo-rotatory, and contains a large per cent of the basic amino-acids.

Caulfield (1935) found several allergically active substances in ragweed pollen. Stull and his associates (1941-1942) found three fractions and studied two. All patients tested reacted to Fraction 1, while some gave little or no reaction to Fraction 2. Sherman found these fractions differ with respect to precipitation by one-half and full saturation with NH_4SO_4 and precipitation with phosphotungstic acid. Their specificity could be demonstrated by passive transfer and by precipitin titre in guinea pigs injected with the fractions. Mosko filtered ragweed extract, boiled it, and precipitated with aluminum cream then washed and filtered. The filtrate contained 1 to $1\frac{1}{2}$ per cent N and as much as 18 per cent reducing substance. Anaphylactic shock could not be produced by the filtrate but results of treatment with the filtrate were as good as with whole ragweed extracts and gave no constitutional reactions. Baldwin precipitated with alcohol and found the alcohol soluble material contained much reducing substance. No precipitins were obtained by these fractions with the high polysaccharide content. The fraction without high carbohydrate content sensitized to whole ragweed although it did not produce precipitins. This extract gave a negative ninhydrin reaction and gave positive skin reactions in non-treated persons.

From the foregoing it may be seen that there is still no unanimity of opinion regarding the nature of the antigenic substance in pollen. Until this is determined all methods of standardization will be more or less empirical and workers will continue the use of the method which seems best to meet their requirements. As long as the active substance cannot be handled as such, as long as solutions deteriorate with age, so long as the content of active material in pollen may vary somewhat with the time and location of its growth, it will have to be kept in mind that extracts made in the same way and standardized by the same method may not be interchangeable and caution must always be used.

CHAPTER XLIX

PRESEASONAL HYPOSENSITIZATION

There are three generally used methods for hyposensitization in pollinosis. Preseasonal or prophylactic treatment was the earliest, naturally so because it duplicated insofar as practicable the experimental production of the state of antianaphylaxis. Coseasonal or phylactic and perennial therapy were introduced later.

Preseasonal treatment.—Cooke stated that the term desensitization is a misnomer, since the patient is not desensitized if the reagin titer may be used as the measure of sensitiveness. Treatment may actually increase this titer. Hypo-sensitization was proposed as a better term. If work with the blocking antibody should prove that it actually is this which protects the patient, we should have to believe that treatment is a process of immunization.

Preseasonal hyposensitization is inaugurated several weeks prior to onset of the season, the initial dose being so small as to cause no symptoms. Subsequent doses are increased in size and given at intervals of several days. Just prior to the onset of the season, the patient receives a top dose which is theoretically slightly below the limit of his tolerance.

Size of first dose.—In the writer's experience 98 per cent will tolerate an initial preseasonal dose of 20 Noon units, corresponding to 0.1 cc. of 1:5,000, 0.2 cc. of 1:10,000, and, roughly, 20 Coea units.

If doubt exists concerning the advisable initial dose, especially in case the diagnostic skin reaction has been unusually intense, the proper initial dose may be determined by skin testing with serial dilutions of extract.

Unusually strong reactions. For this purpose testing should be done endermally with an appropriate diluting fluid (not containing glycerin). The first test dilution should be extremely weak. Let us assume that the diagnostic test was done endermally with 1:5,000 extract. It was very strongly positive. Undoubtedly a ten times dilution or 1:50,000 would still be positive. Therefore, start with 1:500,000 dilution endermally. If this is still positive, test with 1:5,000,000. The dilution may be carried even higher, until one is found at which the reaction is no longer even slightly positive, as compared with a control test with the diluting fluid alone. This first negative dilution represents one with which it is safe to start treatment.

If scratch testing with 1:50 dilution was the diagnostic procedure, the fact that the endermal test is 100 times more reactive than the scratch would place the 1:50 positive scratch in the same category as the 1:5,000 positive endermal which is 100 times more dilute. Therefore, in the presence of a strongly positive 1:50 scratch the same initial dilution would be employed as above; namely, 1:500,000 for endermal serial testing.

Scratch serial testing may be done if preferred, but one should bear in mind that the concentration which first fails to react positively is *not* the one with which to commence treatment. The endermal test being approximately 100 times more reactive, one should start with 100 times greater dilution than is indicated by the serial scratches.

This program is ultraconservative. In the normal routine, a mildly positive 1:50 scratch or 1:5,000 endermal indicates 1:5,000 as the initial concentration.

In other words, one commences with a dilution that has given a positive, rather than negative, reaction. One can usually start with the last positive dilution instead of the first negative. However, an unusually strong test reaction, indicating probable extreme reactivity, justifies extra precautions.

Treatment technic.—Injections are customarily given subcutaneously, but rather superficially, with a tuberculin syringe graduated to 0.01 cc. and a 25 or 27 gauge needle. If a rustless steel needle is used, No. 26 is preferable. If a harder needle is available, No. 27 may be used. A 27 gauge rustless needle bends too easily and has too short a life. This observation also applies to needles used in skin testing.

A tuberculin syringe is preferred since it is often desirable to measure the dose to hundredths of a cc. There is the possibility of confusion in the ordinary tuberculin syringe due to the two graduations, metric and apothecary. This may be a source of real confusion when several persons are treating one patient.

To circumvent this disadvantage Becton, Dickinson & Company have collaborated with the writer in the manufacture of a tuberculin-type precision syringe possessing the following advantages:

1. Only the metric scale is used, with graduations to hundredths of a cubic centimeter.
2. In place of the minim scale there is a coarser graduation in twentieths and tenths.

Since patients who practice self medication, nurses and even physicians are often confused by the two series, a single scale system is preferable.

Schedule of preseasonal dosage.—The initial dose having been given, the following general principles control subsequent therapy.

Injections may be given at weekly or semiweekly intervals. An interval of longer than one week is not desirable since there is a gradual loss in the hyposensitization that has been achieved, after longer periods. Oftener than twice weekly is not desirable, especially when higher doses have been reached, since Cohen and his collaborators have shown that injected pollen allergen continues to circulate as such in the blood for at least 48 hours. It is usually gone at the end of 72 hours. Daily injections might therefore have a cumulative effect, eventually resulting in constitutional reaction. Injections every second day, that is, with one day intervening, would be marginal as regards this possibility. Injections every three or four days or twice weekly have in my experience failed to show any evidence of cumulative action.

Avoidance of reactions.—This precaution is to be stressed especially with those patients who come in too late before the onset of the pollen season. In such cases there is a temptation to increase the dose rapidly. While this can often be done with safety, there is greater risk of constitutional reaction, and the procedure should be avoided. Either of two substitute programs may be adopted. The patient may be informed that it is too late to achieve adequate preseasonal treatment and that it would be better for him to wait until the onset of symptoms, when he is to report for coseasonal therapy. Or, the patient may be told that it is too late to achieve the desired top dose but that treatment may be given twice weekly with the usual increase. An adequate top dose will not be reached prior to the season and coseasonal treatment will probably also be required, but the partial hyposensitization given prior to the season will probably make coseasonal treatment more effective.

Rapid increase in dosage may be more safely carried out with the higher dilutions, that is the earlier injections, than with the more concentrated. Early in the course, the dose may safely be doubled each time. Later, the increase should be more gradual. For the average case the schedule shown in Table XXXIX is adequate.

TABLE XXXIX.—SCHEDULE OF PRESEASONAL TREATMENT

INJECTIONS TO BE GIVEN ONCE OR TWICE WEEKLY			
INJECTIONS	DILUTION	DOSE IN CC.	NOON UNITS
1st	1:5,000	0.1	20
2nd	1:5,000	0.2	40
3rd	1:5,000	0.4	80
4th	1:500	0.07	140
5th	1:500	0.1	200
6th	1:500	0.2	400
7th	1:500	0.4	800
8th	1:50	0.06	1,200
9th	1:50	0.08	1,600
10th	1:50	0.1	2,000
11th	1:50	0.2	4,000
12th	1:50	0.3	6,000
13th	1:50	0.4	8,000
14th	1:50	0.5	10,000
15th	1:50	0.6	12,000
16th	1:50	0.7	14,000
17th	1:50	0.8	16,000
18th	1:50	0.9	18,000
19th	1:50	1.0	20,000

This is, in the writer's experience, a very safe schedule. It provides a course of 19 injections which, if given twice weekly, necessitates the institution of treatments about ten weeks prior to the season. This may safely be reduced to the following series of 14 injections, requiring 7 weeks.

TABLE XL.—ALTERNATE SCHEDULE

INJECTIONS TO BE GIVEN TWICE WEEKLY			
INJECTIONS	DILUTION	DOSE IN CC.	NOON UNITS
1st	1:5,000	0.1	20
2nd	1:5,000	0.2	40
3rd	1:5,000	0.4	80
4th	1:500	0.07	140
5th	1:500	0.1	200
6th	1:500	0.2	400
7th	1:500	0.4	800
8th	1:50	0.07	1,400
9th	1:50	0.1	2,000
10th	1:50	0.2	4,000
11th	1:50	0.4	8,000
12th	1:50	0.6	12,000
13th	1:50	0.8	16,000
14th	1:50	1.0	20,000

With mild allergies one may safely start with a larger dose such as 200 units, thus eliminating the first four injections. However, I have on rare occasions seen reactions following 20 or 40 units in patients who showed only very mildly positive skin reactions, and therefore do not recommend this procedure. These reactions have not been of the explosive constitutional type, but have consisted of malaise, possibly pyrexia, soreness in the injected arm.

Injections of 1:5,000 may safely be given every day provided the delayed subcutaneous reaction to be described later does not occur. Subsequent treatment with 1:500 concentration may be given every third day; 1:50 concentration should not be given oftener than twice weekly. With the average patient the dose may be doubled each time, only with the weaker dilutions. Application of these rules provides the *shortest schedule* in which a patient may be adequately hyposensitized preseasonally, to reach a top dose of 20,000 units. This requires slightly over five weeks, with treatments on Sunday when indicated; the patient remaining in the office at least thirty minutes after each injection to control any possible subsequent reaction. There may be delays anywhere along the line due to persistence of subcutaneous reactions.

TALBLE XLI.—RAPID PRESEASONAL HYPOSENSITIZING PROGRAM

DAY	DILUTION	VOLUME IN CC.	NOON UNITS
1st	1:5,000	0.1	20
2nd	1:5,000	0.2	40
3rd	1:5,000	0.4	80
4th	1:500	0.06	120
5th	1:500	0.08	160
8th	1:500	0.1	200
11th	1:500	0.2	400
14th	1:500	0.4	800
17th	1:50	0.07	1,400
20th	1:50	0.1	2,000
23rd	1:50	0.2	4,000
27th	1:50	0.4	8,000
30th	1:50	0.6	12,000
34th	1:50	0.8	16,000
37th	1:50	1.0	20,000

Small volume.—It is desirable to keep the volume of each injection below 0.5 cc., especially when extracts containing glycerin are given, because of the pain accompanying larger quantities. With most persons this is negligible, but some complain of it. In the preceding tables the volume is less than 0.5 cc. except with 1:50 dilutions. If one desires to apply the principle with the high concentrations, 1:25 or 1:10 extract should be made up. The following conversion table may then be applied to the preceding schedules.

TABLE XLII.—CONVERSION TABLES 1:50 TO 1:10

NOON UNITS	1:50 IN CC.	1:25 IN CC.	1:10 IN CC.
1,000	0.05		
1,200	0.06	0.03	
1,400	0.07		
1,600	0.08	0.04	
2,000	0.1	0.05	0.02
4,000	0.2	0.1	0.04
6,000	0.3	0.15	0.06
8,000	0.4	0.2	0.08
10,000	0.5	0.25	0.1
12,000	0.6	0.3	0.12
14,000	0.7	0.35	0.14
16,000	0.8	0.4	0.16
18,000	0.9	0.45	0.18
20,000	1.0	0.5	0.2
30,000	1.5		0.3
40,000			0.4
50,000			0.5

Not all allergists agree with these schedules. Cooke, Vander Veer and Barnard have recommended the following standardized desensitization therapy for pollens, based upon the Cooke and Stull protein unit.

Program of Cooke, Vander Veer and Barnard. The degree of sensitization is determined by intracutaneous tests with extracts of varying concentration. A strong intracutaneous reaction to an extract so dilute that it contains only 10 protein units per cc. indicates a strongly sensitized case. If a similar strong reaction is observed, not to 10 units per cc., but to 100 units per cc., sensitization is moderate. If this strong intracutaneous reaction is not observed until the test solution strength has been increased to 1,000 units per cc., the case is relatively insensitive.

The extremely sensitized patient should start with a very small dose, 5 units being suggested. The moderately sensitized may start with 10 units, while the mild allergic may start with 50 units. In Table XLV, suggested dosages for preseasonal treatment, Cooke, Vander Veer and Barnard provide a top dose of 1,000 protein units for the strongly reactive, 5,000 for the moderate, and 20,000 for the mild.

Top dose protection.—There is some evidence suggesting that provided we could safely give the required top dose or maximum dose at the beginning, the patient would be adequately protected with a single injection. There are records of patients who have, through error, received a very large dose without previous injections at or near the onset of the season, who have had severe constitutional reactions and who have thereafter passed through the entire season without further treatment and without symptoms. Such cases constitute the clinical counterpart of experimental antianaphylaxis in which sensitized animals, having received doses of antigen which are just sublethal, have, following recovery, been completely protected against anaphylactic shock. However, this procedure is too dangerous to apply to humans. Fortunately, the preseasonal method of gradually building up the dose works satisfactorily. This treatment over a matter of several weeks constitutes, as I see it, a gradual process of acclimatization to a new environment, or more accurately a new element in the environment. In this sense it is comparable to acclimatization or desensitization in allergy to heat or cold.

Adequate top dose.—The principle governing preseasonal therapy is that, starting with a dose so small as to produce no symptoms, this is increased until one is reached which still causes no symptoms but which has acclimatized the tissues to ragweed allergen so that, when contact occurs in the natural way, there will still be no symptoms. This ideal is sometimes achieved. Often it fails for one reason or another, but rarely to any great degree. As we have seen, the first dose may produce symptoms. The proper dose anywhere along the series may cause symptoms. The desired top dose may be above the patient's tolerance. Then, the highest doses cause symptoms. Finally, even though one may have carried the patient completely through preseasonal hyposensitization without symptoms, treatment may be inadequate to protect against those days during the season when the atmospheric pollen concentration is unusually high.

It has been abundantly demonstrated that of all the factors which may influence the results of pollen therapy, the reaching of an adequate top dose or protective dose preseasonally is the most important. In the early days of therapy a top dose of 2,000 to 4,000 Noon units of ragweed extract was considered adequate by observers working chiefly in the northeastern states.

TABLE XLIII. SUGGESTED DOSAGE PRESEASONAL TREATMENT WEEKLY INJECTION
(Cooke, Vander Veer and Barnard.)

VERY SENSITIVE CASE				MODERATELY SENSITIVE CASE				RELATIVELY INSENSITIVE CASE			
Dosage		Bottle	Amount	Dosage		Bottle	Amount	Dosage		Bottle	Amount
Prot. N.	Units			Prot. N.	Units			Prot. N.	Units		
MG.			CC.	MG.			CC.	MG.			CC.
0.00005	5	50 units per cc.	0.1	0.0001	10	100 units per cc.	0.1	0.0005	50	500 units per cc.	0.1
0.0001	10		0.2	0.0002	20		0.2	0.0015	150		0.3
0.00015	15		0.3	0.0004	40		0.4	0.003	300		0.6
0.00025	25		0.5	0.0007	70		0.7	0.005	500		0.1
0.00035	35		0.7	0.001	100		0.1	0.0075	750		0.15
0.0005	50	250 units per cc.	0.2	0.002	200	1,000 units per cc.	0.2	0.01	1,000	5,000 units per cc.	0.2
0.00075	75		0.3	0.004	400		0.4	0.015	1,500		0.3
0.00125	125		0.5	0.007	700		0.7	0.025	2,500		0.5
0.00175	175		0.7	0.01	1,000		0.1	0.04	4,000		0.8
0.0025	250		1.0	0.015	1,500		0.15	0.06	6,000		0.3
0.003	300	2,000 units per cc.	0.15	0.02	2,000	10,000 units per cc.	0.2	0.08	8,000	20,000 units per cc.	0.4
0.004	400		0.2	0.03	3,000		0.3	0.1	10,000		0.5
0.006	600		0.3	0.04	4,000		0.4	0.12	12,000		0.6
0.008	800		0.4	0.05	5,000		0.5	0.14	14,000		0.7
0.01	1,000		0.5					0.16	16,000		0.8
								0.18	18,000		0.9
								0.2	20,000		1.0

Until within recent years preseasonal treatment sets dispensed by commercial houses carried only this top dose. This explains frequent failure to gain adequate relief from these preparations.

The writer finds that in Virginia adequate relief may be obtained with a top dose of 20,000 Noon units or 1 cc. of 1:50 extract. Here again the conclusions reached by various allergists differ. In the survey by Alexander previously referred to, 56 allergists reported their optimal maximum dose for the average case; 45 preferred top doses of 10,000 units or less, the lowest being 2,000; 11 preferred 20,000 or more, the highest being 100,000 units or 1 cc. of 1:10 concentration. A top dose of 100,000 units was recommended by one allergist; 50,000 by two; 30,000 by two; 25,000 by one; and 20,000 by five. Alexander's report did not indicate whether those with lower top doses reported as good results as those with the higher doses.

There is a tendency among allergists to give higher top doses than formerly. When I first recommended 20,000 Noon units as the desirable top, some allergists felt that this was dangerously high. Since then a large number have come to use the same top dose. Some use much higher dosages. G. T. Brown, for instance, reaches a top of either 60,000 or 100,000 Noon units. I see no reason why the dose should not be increased provided the patient does not develop intolerance at some place along the schedule. One reason for having stopped at 20,000 units was that this represented 1 cc. (a fairly large volume for subcutaneous administration, as far as the comfort of the patient is concerned) of a 2 per cent extract. It has been maintained that one cannot make an extract stronger than 2 or 3 per cent (Piness, Huber, Black). Therefore, 1 cc. of 1:50 extract represented about as large a dose as could conveniently be administered. Brown maintains that extracts up to 12 per cent concentration show proportionate amounts of nitrogen and of activity. That is, a 12 per cent extract is 12 times as strong as 1 per cent. Others (mentioned above) have been unable to confirm this and state that a 12 per cent extract is little stronger than 2 or 3 per cent. Recently Cooke has concluded from protein nitrogen determinations that 9 per cent extract is 9 times as strong as 1 per cent. He went no higher than 9 per cent in his studies. Brown's highest concentration is what he considers a true 10 per cent extract. His highest dose is 1 cc. His highest dose in terms of Noon pollen units, therefore, would be 100,000 units. He takes a longer period for hyposensitization, beginning preferably about six or more months before the onset of the season. After the termination of the season he continues with perennial treatment.

In Brown's experience quantitative extraction can be accomplished up to 12 per cent. Above 12 per cent the extraction is no longer quantitative, there being a steady falling off in the proportion extracted. He found that 17.5 per cent extract was no more highly antigenic than 12.5 per cent.

Sullivan and Vaughan (1939) find 10 per cent extracts five times as strong as 2 per cent extracts.

Brown has demonstrated that in competent hands the preseasonal ragweed dose may be carried much higher than is customary, without unpleasant reactions and has reported excellent results. The dose should be made high enough to obtain best results. There is no need in carrying it higher. Possibly more than 20,000 or 30,000 units would be more efficacious, but doses exceeding this are not customarily used by most allergists.

Waldbott and Ascher have confirmed Cooke's observation that, with stronger skin reactions, lower top dosage is efficacious. These observers di

vided their cases into five groups, depending upon the intensity of the skin reaction. In group one, the most reactive, an intracutaneous dose of 1.5 Noon units produced a wheal 2.5 centimeters in diameter. In the least reactive group, 15 or more units were necessary to produce the same size wheal. Intervening groups required intervening dosages. They found that group one experienced 50 per cent relief from a preseasonal top dose of approximately 1,000 units, while group 5 required almost 5,000 units for equal relief.

The highly reactive group obtained 80 per cent relief with top dose 3,200 units as contrasted with the 10,000 units required for the least reactive group. However, for more complete relief the requisite top doses approach each other in both, and in the intervening groups. For 98 per cent relief about 5,700 units were required by group 1, 13,200 for group 5. For 95 to 100 per cent, a preseasonal top dose of approximately 10,000 units was required by group 1, 16,000 by group 2. When 18,000 units were given, all groups experienced more than 95 per cent relief.

These observations would indicate that from 10,000 to 20,000 pollen units top dose is required in an average season in Detroit. The season studied showed an average daily pollen count of 400 during the peak week with a single maximum of 600.

Waldbott and Ascher conclude that 15,000 to 20,000 units achieve maximum relief for their patients. In some cases they gave considerably higher doses, reaching in one case 220,000 units top dose, comprising 90,000 units of giant ragweed, 90,000 of short, 20,000 units of cocklebur and 20,000 of marsh elder. They found that doses above 15,000 units did not seem to give greater benefit; that cases with intense skin reactions should not be subjected to too vigorous treatment, certainly not above 15,000.

No amount of preseasonal treatment will prevent symptoms from gross overdosage. A young boy usually had asthma from ragweed so severely in the autumn that he missed three or four weeks from school. Following his first course of preseasonal desensitization he was completely relieved, with no asthma until the day before school opened. This was a keen disappointment since he did not wish to attend school. On that day his mother found him in the back yard rubbing his face in ragweed. He developed a severe acute conjunctivitis, hay fever, ragweed dermatitis of the face and asthma which required his spending several days in bed.

Variations in size of top dose. The ideal top dose varies somewhat with different pollens. While I find 20,000 units desirable in ragweed prophylaxis, 10,000 units, or even 6,000 or 4,000, are adequate for protection against the less toxic grass pollens.

Occasionally, a person will not tolerate a top ragweed dose of 20,000 units. I have seen not over a dozen such in 18 years of allergic practice. These persons may break tolerance almost anywhere along the preseasonal program but in my experience they usually break at around 2,000 to 4,000 units. One patient whom I had followed for five years, treating her sometimes preseasonally, sometimes perennially, and whom I had never succeeded in building up to more than 4,000 ragweed units preseasonally, was run up without any difficulty whatsoever to 10,000 units prior to the 1937 ragweed season. In this season she obtained more relief than in any previous season. This might be interpreted as due to the higher top dose were it not that the 1937 pollen season was one of the mildest we have had.

With patients who manifest symptoms from a lower dosage and who, after several trials, continue to do so, it is better to keep the dose just below

this point than to attempt to force it higher. As a rule, the results are good. If they are not, supplementary coseasonal treatment may be given.

According to Cooke and Vander Veer the amount of pollen extract which must be given for preseasonal control may be predetermined by the size of the original endermal reaction. These observers classify cases according to the intensity of the reaction to various dilutions. The class A or extremely sensitized patient gives a marked intracutaneous reaction to a concentration of 0.0001 mg. total nitrogen per cc. The class C patient gives a marked reaction with a concentration of 0.01 mg. per cc. The former, highly sensitized, does not need as many injections as the latter nor need the top dose just prior to the season to be anywhere near as high as for the very mild case. These authors believe that patients with extremely strong skin reactions are adequately protected with smaller top doses than those giving mildly positive skin reactions.

For the past few years Hansel has used very small doses throughout the period of treatment. He may begin treatment with as small an amount as 1 to 10 million dilution and the maximum dilution reached may be 1 to 10 thousand. The general technic of treatment is the same as that described in this chapter except that the doses are on an entirely different order of magnitude. Hansel believes that the results of such treatment are probably better than those obtained by the use of larger doses.

Treatment during the season. -Preseasonal hyposensitization terminates with the onset of the season. Strictly speaking, no injections are to be given thereafter. If symptoms develop in spite of preseasonal hyposensitization, small dosage coseasonal treatment may be given entirely independently of the previous therapy. If perennial treatment is to follow, injections should be continued every two weeks through the season. But under no circumstances should they be as large as the top preseasonal dose. If the top dose was 20,000 units, perennial dosages during the season should drop to 2,000 or 4,000 units or 0.1 or 0.2 cc. of 1:50 concentration. The objective of pre-seasonal treatment has been to expose the patient to such an amount of the allergen that he can tolerate normal exposure. There is no need for continuing large doses. Otherwise, we are forcing him to attempt to tolerate a combined exposure (atmospheric and parenteral) to which he has not been accustomed. The only reason for giving any injections of concentrated extract (2,000 to 4,000 units) would be as a preliminary to perennial treatment, to prevent the gradual loss of tolerance established just prior to pollination. Experience has shown that this loss is gradual, that it is insignificant at the end of one month but recognizable after two months. Since the pollen season usually does not last more than six or eight weeks, and since the loss of tolerance is not great over this interval, there is no need for continuing high dosages. If perennial treatment is not to follow preseasonal, no injections need be given during the season as long as the patient continues relieved. Specific treatment appropriate in the season is described under coseasonal and perennial therapy.

Many of those who use preseasonal treatment do not think it safe to discontinue treatment during the season but continue with somewhat reduced dosage. Especially in the south where the seasons are long they believe that some treatment should be maintained. Colmes (1945) found that in Boston the patients who received adequate preseasonal ragweed therapy did as well with no coseasonal treatment as did a control group who received treatment through the season.

CHAPTER I

REACTIONS

Several varieties of reactions may occur during pollen therapy. While some are of little importance to the therapist, all are important to the patient. Every effort should be directed toward avoiding any type of reaction.

Subcutaneous reaction.—This is the most frequent. It is a delayed reaction, coming on after several hours and lasting from 12 to 24 hours or longer; manifested by induration, swelling, local heat, redness and tenderness, somewhat resembling a beginning local cellulitis. The area involved may vary from one or two centimeters around the site of injection to the size of one's palm or may rarely involve the entire arm. The reaction is chemical, without associated infection and subsides spontaneously in a day or two.

As a rule the subcutaneous reaction is specific, indicating allergy to the injected substance. Its specificity has been recognized by Kahn who recommended it as a diagnostic procedure in cases of pollinosis where skin tests have been negative. Kahn, living in Texas where pollen of one variety or another is in the air practically throughout the year, and where pollen allergy may be perennial, finds the subcutaneous test of value in the recognition of very mildly sensitized pollen allergies. But in treatment, the subcutaneous test of Kahn becomes an undesirable reaction. In general, it may be said that when a subcutaneous reaction has occurred, no further treatment should be given until the reaction has subsided.

A nonspecific subcutaneous reaction is occasionally encountered when glycerin extracts are used. A small percentage appear to react to subcutaneous glycerin with a response similar to that above described. This is usually observed early in treatment, after the first two or three injections of a very dilute solution. In such cases a change to an extract in Coca's fluid or other menstruum not containing glycerin, results in disappearance of this delayed reaction. This response requires a change of extract, whether the treatment be preseasonal, coseasonal or perennial, if it causes too great discomfort.

Toxic reaction.—This occurs in a small proportion and may be specific or due to some other entirely unrelated etiology such as the onset of an acute head cold, the ingestion of an allergenic food, etc. At the next treatment the subject remarks that the last one made him dozey, headachy, feverish; made him feel generally wretched, as though he were coming down with a cold. It is usually difficult to assign a definite etiology to these symptoms which may be coincidental, but they occur just often enough to give the impression of being a true reaction. As a rule if treatment is persisted in, this response disappears rather than becoming more pronounced.

Coincidental reactions. Anything that happens to the patient who has received a therapeutic injection may be attributed by him to the injection. A patient had crops of boils shortly after hyposensitization was instituted. No local reaction occurred. He was reassured with the fact that boils are infectious and that he had no infection at the site of injection. Any sort of nervous or psychogenic symptoms may be attributed by the patient to hyposensitization. These are controlled by an explanation of the mechanism of treatment and the impossibility of such symptoms resulting therefrom.

Infection.—In eighteen years with an unrecorded number of thousands of skin tests and therapeutic injections we have never had an infection from skin testing and only two local abscesses following treatment. Rarely a sterile abscess may occur probably as a result of a mechanism similar to the Arthus phenomenon. We have seen two of these. Both appeared after a considerable number of subcutaneous injections over a period of several weeks, and both were shown to be sterile by culture. Occasional instances of necrosis following sterile injections have been reported and are probably analogous reactions.

Systemic reaction.—Systemic and constitutional reactions are the *bêtes noires* of the allergist. Every effort must be exerted toward their avoidance. The former is a localized or low-grade manifestation of the latter.

It is well to explain early in treatment that following some injection there might be mild symptoms, an attack of hay fever, a short asthmatic episode, or hives. It is therefore desirable that the patient remain in the office for thirty minutes after each injection so that if such episodes occur treatment can be given promptly with equally prompt relief. A reaction which occurs after thirty minutes is relatively milder. However, any of these symptoms may occur after intervals up to two hours or longer and for this reason it is well for the patient to have some ephedrin capsules ($\frac{3}{4}$ th grain) with him at all times during the course of treatment. He is directed to take one at once on the advent of symptoms and to return to the office without delay for adrenalin treatment. If he understands beforehand the possibility of systemic respiratory or cutaneous manifestations, he will not be surprised or alarmed, will take his ephedrin, and return for relief. Often the ephedrin has relieved him by the time he reaches the office, in which case he is directed to repeat it if symptoms return. If he is not adequately relieved upon arrival, epinephrin 1:1,000, 0.3 to 0.5 cc., gives relief. It should be given in the arm which did not receive the pollen extract. If symptoms are urgent, a tourniquet may be applied above the site of inoculation as described in the next section. In my experience reactions occurring after two hours are always systemic, involving one or more shock tissues, especially the nose, the bronchial tree or the skin, and never become constitutional or generalized as in anaphylactic shock. Rarely the shock tissue is the gastrointestinal tract, reacting with nausea, vomiting or diarrhea. Any busy allergy clinic will encounter from one to a half dozen systemic reactions each season. They may occur at any point during the schedule of preseasonal treatment. It is some consolation to the patient to know that especially if systemic reaction has occurred toward the end of treatment, the chances are that he will obtain especially good results during the season.

When systemic reaction has occurred, the cause should be sought. Possibly the therapist has been overenthusiastic, increasing the dose too rapidly or giving injections too frequently. Experience indicates that extreme heat or unusual exercise during the first hours after injection predisposes to systemic or constitutional reactions and the patient is well advised to be quiet for a time after treatment. The possibility of accidental "subcutaneous" injection directly into a vein or venule must be accepted although I must confess to never having seen a reaction definitely attributable to such a circumstance. However, the precautionary measure suggested by Bernton is so easy of application that it should not be neglected. This consists in introducing the needle rather superficially under the skin and, before pushing

the plunger home, tugging gently on it to see whether blood is drawn back into the syringe. If it is, the needle is withdrawn and inserted in another location.

It is a safe precaution to ask the patient prior to each injection whether he had any unusual symptoms following the last one. If he did, the next dose should not be increased; indeed, it is better reduced.

In the event of systemic or constitutional reaction the next subsequent dose should be of diminished size. A reduction to one-half the previous pollen unit dose is generally considered safe. From this point, increases are made in accordance with the regular schedule. If, however, reactions again occur, the same reduced dose may be given several times, following which subsequent injections are given with decidedly smaller increments. Where a definite tendency is manifest in the occurrence of repeated systemic reactions, epinephrin 1:1,000, 0.3 cc., may be given with each injection. Experience has indicated and Feinberg and Bernstein have shown experimentally that this procedure delays absorption but does not impair antigenic activity of the extract. The delayed absorption over a longer interval tends to prevent systemic reaction, delays its appearance, and makes it milder.

Constitutional reaction. Allergic shock. Anaphylactic shock.—This fortunately rare reaction is, I believe, different from the systemic reaction just described. The latter is generalized in the sense that it involves tissues remote from the site of inoculation, but is still localized to certain of the shock systems. Symptoms of this type of reaction almost invariably commence with urticaria, sneezing or asthma.

The constitutional reaction or acute anaphylactic shock appears to involve all tissues simultaneously, or at least, often manifests itself without localizing symptoms at the outset. It may come on immediately after an injection or after a short interval, rarely longer than thirty minutes. At the onset the patient complains of a sudden sense of great uneasiness, anxiety, pounding headache and intense throbbing in the ears. The first manifestation may be collapse. The picture is of deep generalized shock. The patient may become unconscious at once or more gradually. He does not always lose consciousness. Death may occur almost at once. After an interval gradual recovery may ensue. Pulmonary symptoms, if present, are more likely to be those of acute pulmonary edema than of bronchial asthma. It is as a rule not until the stage of recovery that *systemic* symptoms, urticaria and asthma, appear.

We have seen that an outstanding pathologic response in allergy is markedly increased capillary permeability. The writer visualizes the acute reaction in human anaphylactic shock as due to a sudden, generalized, almost universal capillary hyperpermeability, involving not only allergic shock organs but other tissues as well. The rapidity with which such a response can occur may be understood in view of the following facts. The surface area of the capillaries in the muscles alone is 3,000 times the surface area of the skin. It has been calculated that if all restraining forces were withdrawn, the entire plasma volume could pass from the capillaries into the body tissues within ten seconds. Water comprises 70 per cent of the total weight of the body. Fifty per cent is retained within the cells, 5 per cent in the blood vessels, and 15 per cent is in the tissue spaces, but extracellular. There is a close balance between this extracellular tissue fluid and the intravascular fluid. It becomes obvious that the transfer of only a small proportion of

the total body fluid, not more than 2.5 to 7 per cent, would be sufficient to produce severe shock or death. The transfer of 7 per cent of the total fluid into the tissue spaces would mean its complete removal from the blood, assuming that there is no change in its concentration in the living cells.

The constitutional reaction is to be guarded against under all circumstances. Several deaths have been reported in the literature from this cause, although many more are associated with serum administration than with pollen injections. Most anaphylactic deaths occurred early in the development of allergic therapy. The methods in use today have been designed to safeguard against it. When constitutional reaction does occur, this can almost invariably be traced to an error in technic.

The prevention and control of constitutional reactions in pollen therapy will be discussed in the chapter on anaphylactic shock.

Rappaport* calls attention to delayed "constitutional" reactions coming on from 1 to 12 hours after inoculation and consisting of headache, nausea, occasional vomiting, achiness, chilliness, malaise, and a temperature rise of 1 or 2 degrees. Local swelling at the site of injection is always large. No urticaria, asthma, or hay fever occurs. Symptoms subside in 24 to 48 hours. Adrenalin promptly relieves symptoms. This is not unlike the toxic reaction mentioned above.

*Rappaport, Ben Z., Chicago. In the International Correspondence Club of Allergy.

CHAPTER LI

COSEASONAL POLLEN THERAPY

In 1921 Walker summarized the appropriate treatment of pollinosis. He stated that in those cases showing little or no improvement, pollen extract injections may be continued, but in smaller amounts, given at the same intervals of from 5 to 7 days. In some cases the symptoms were made worse by the injection of pollen extract during the hay fever season.

During the 1922 season, three patients whom the present writer had treated preseasonally, did have symptoms during the season sufficiently severe to require relief. Following Walker's suggestion, treatment was continued during the season, with two important modifications. First, injections were given each day instead of at from five- to seven-day intervals, and second, the dose was reduced much more than recommended, to practically the initial preseasonal dose. The philosophy of the procedure at the time was the eventual administration of the full amount, but in divided doses. In all three cases improvement was prompt. With relief of symptoms the small injections were given at less frequent intervals, ultimately discontinued. In some instances symptoms returned after discontinuance but were again promptly relieved following daily injections of minute amounts.

The success achieved led me to attempt similar treatment with two additional patients who came in for the first time with symptoms during the season. They had received no preseasonal treatment. Results were equally good. Since these observations were reported, many allergists have presented confirmation of the value of coseasonal treatment and the procedure has become recognized in routine pollen therapy.

Difficulties.—My own experience subsequent to 1922 was of particular interest. While the 1922 results were surprisingly good, those from then through 1930 were never quite as satisfactory. In 1930, 71 per cent of pollinosis cases obtained satisfactory results from preseasonal treatment while but 60 per cent were relieved with coseasonal treatment only. We had been rather perplexed at this failure to repeat the better results of 1922 until we realized that we were giving larger doses coseasonally. The 1922 doses had been timid ones. Those in succeeding years were bolder. Indeed, we were attempting to build up the dosage coseasonally very much as is done preseasonally. This procedure is still being followed by many allergists. It was not that which was originally used in 1922. In the pollen season 1931 we returned to our original procedure of minute doses, kept small. The results were as satisfactory as in 1922, and have continued so since. In 1931, 85 per cent obtained 75 per cent or more relief from preseasonal treatment, while 87 per cent received comparable benefit from coseasonal treatment alone.

Rationale. The rationale of coseasonal treatment appears to be altogether different from that of preseasonal. In the latter, success depends upon reaching a high top dose just prior to the onset of the pollen season. With coseasonal therapy, adequate relief is obtained in a large proportion with a top dose of not more than 80 pollen units. The principle of coseasonal therapy

is that of frequent small doses, kept small. We have obtained as good results with pollen asthmatics as in pollen hay fever, provided the principles listed in the discussion of preseasonal therapy are followed, namely, that foods and other inhalants must also be considered.

CASE REPORTS.—The following case records illustrate results to be anticipated. They are from the 1931 season just mentioned. It will be seen from Fig. 104 that this season was one of relatively high pollen prevalence, decidedly higher than that for 1930 (Fig. 103) in which coseasonal results had been by no means as satisfactory.

Mrs. T., ragweed hay fever, started treatment September 1, 1931, with ragweed 20 units (1:5,000, 0.1 cc.), and adrenalin-ephedrin mixture 0.3 cc.

September 2	Very much improved.
September 3	Doing nicely, having but little sneezing. Rx. ragweed 20 units.
September 5	Backsliding a bit. Rx. 40 units with adrenalin-ephedrin.
September 8	Did splendidly after last treatment but has flared up in the last eighteen hours. Rx. ragweed 80 units.
September 9	A little return of trouble, not much. Rx. ragweed 80 units.
September 13	Doing nicely. Rx. ragweed 80 units.
September 14	Still doing nicely. Rx. ragweed 80 units.
September 15	Doing splendidly. Had some hay fever last night and says this is the only time she has really had any hay fever at all since she started coming. Rx. ragweed 80 units.
September 17	Doing nicely. Rx. ragweed 80 units.
September 19	Not doing so well. Rx. ragweed 80 units.
September 21	Doing satisfactorily. Rx. ragweed 80 units.
September 23	Doing splendidly. No symptoms. Rx. ragweed 100 units.
September 28	Doing nicely. Rx. ragweed 80 units.

From this time on the patient had no symptoms whatsoever, continuing with weekly injections which at the end of the season were gradually increased for perennial therapy.

Mr. B., ragweed hay fever, first dose 20 units, September 4, 1931.

September 5	Possibly a little better. Rx. 60 units.
September 8	No improvement except that he was a little better after the first injection. Rx. 60 units.
September 9	Doing splendidly. Says that the results are excellent so far. Rx. ragweed 80 units.
September 10	Doing fine. Fully 75 per cent relieved so far. Rx. 80 units.
September 11	Doing splendidly. Delighted with results. Rx. 100 units.
September 14	Ninety per cent relief. Rx. 80 units.
September 16	Relief continued. Rx. 100 units.
September 18	No trouble. Rx. 80 units.

This was followed by injections of 80 to 100 units every second or third day until September 29 when the patient went on weekly therapy with gradually increasing doses for perennial treatment. Five days after the institution of treatment he was 75 per cent improved. Four days later he was 90 per cent improved by his statement, and relief continued throughout the season.

Mr. G., ragweed hay fever, first seen September 8, 1931, at which time he received 20 units of ragweed extract.

September 9	Distinctly better. Rx. 40 units.
September 10	Distinctly better. Rx. 60 units. Omit milk, coffee, banana and asparagus from diet.
September 11	Seventy-five per cent relieved. Rx. 80 units.
September 14	Doing nicely. Has had a little flare-up over the week-end. Rx. 80 units.
September 16	Not quite so well. About 50 per cent relief. Rx. 120 units.
September 17	Doing better again. Rx. 120 units.
September 18	Temperature 100.2°. Has a beginning head cold. Rx. rhinopathogen vaccine.
September 19	Temperature normal. Much better. Rx. ragweed 100 units.
September 22	Doing fine. Practically free from symptoms. Rx. ragweed 100 units.

September 24	Patient had considerable headache yesterday and one antrum was opened. No pus, but the headache was at once relieved. Rx. ragweed 120 units.
September 26	Much better. Rx. ragweed 120 units.
September 28	Doing nicely. Rx. ragweed 120 units.
September 30	No symptoms. Rx. ragweed 100 units.

The patient had no return of symptoms and from this last date started on weekly therapy with increasing dosage for perennial treatment.

Mr. Y., first seen August 25 and given ragweed 20 units.

August 26	No change. Rx. ragweed 40 units.
August 27	Doing fairly well although he had some hay fever. Rx. ragweed 80 units.
August 28	Patient had a reaction with urticaria about one hour after receiving his last dose of 80 units. Rx. ragweed 140 units.
August 31	Having considerable hay fever. Rx. ragweed 100 units.
September 1	Doing reasonably well. Rx. ragweed 140 units.
September 2	Doing nicely until about 4 P.M. today when he became suddenly stopped up and has had rather bad hay fever. Rx. ragweed 180 units.
September 4	Still having some sneezing. Rx. ragweed 200 units.

The patient did not return for one month.

October 5	Patient comes in to report he got through the ragweed season beautifully and has had no trouble since the last note of September 4. Note that this intervening period includes the peak of ragweed prevalence for the season.
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This case exemplifies the need for small dosage in coseasonal therapy. The addition of a relatively very small dose of pollen extract to the amount already being absorbed through the respiratory tract was sufficient to produce a mild, generalized reaction manifested by urticaria.

Anderson (1932) using the principle of small doses frequently repeated, as outlined by Vaughan, reported good results from coseasonal treatment. In a series of 135 cases the average relief for all cases was 80.3 per cent.

Mechanism.—I have no adequate explanation for the good results from small dosage coseasonal therapy. Preseasonally, the top dose must be high; coseasonally it must not be high. Relief is obtained with 1/250th or even 1/500th of the requisite preseasonal dose. The process is not one of antibody exhaustion, since patients relieved with minute doses still give positive skin and ophthalmic reactions, and still react positively by passive transfer. There is still abundant reagin in the blood. This, of course, is also true, although often in lesser degree with preseasonal therapy. Bearing in mind that pollinosis is a constitutional disease, not a local one, and that during the pollen season the nasal or respiratory mucosa is bearing the brunt of the allergic reaction, one might theorize that the administration of small amounts of pollen elsewhere, as through the skin, would distribute the reaction to some extent through the other tissues, thereby relieving some of the intensity of the local mucous membrane reaction. However, this is not an altogether acceptable explanation in terms of present-day concepts of the mechanism of allergy. The fact, though unexplained, remains. We have been able to apply it with success in some other forms of allergy.

Endermal treatment. Following the introduction of coseasonal treatment in 1923, Phillips (1926 and 1933) reported favorable coseasonal results with intracutaneous rather than subcutaneous injections. According to his method

of classification 91 per cent obtained satisfactory relief. He designated only two groups, satisfactory and unsatisfactory. By satisfactory he implies the attainment of adequate relief, sufficient for the patient to continue his usual activities, notwithstanding an occasional symptom. It is difficult to compare these statistics, since 50 per cent relief in one individual might be considered satisfactory while 75 per cent in another might be classed as unsatisfactory. However, aside from this difficulty it is an entirely reasonable method of classification and Phillips' reports may be accepted as indicating very good results from coseasonal treatment.

The question arises as to which is preferable, subcutaneous or intracutaneous injections. I personally prefer the subcutaneous method for reasons which will be presented shortly, and use the dermal method only in cases of tree sensitization where the pollen period is very short, ten days or two weeks, and when we can obtain adequate relief by the simple procedure of doing a scratch test with concentrated 1:50 pollen extract each day. The patient is able to do this himself at home. When the tree pollen period is longer we use subcutaneous small dosage therapy.

The criticism has been raised of intracutaneous treatment, that there is more danger of constitutional reaction and danger of scarring from the injections. The skin is an immunologic tissue, developed in part for the purpose of protection, and there is close coordination between the skin itself and the mechanism of immunologic or allergic response. Whether this integration is through the nervous system or through the blood or lymphatics remains unknown. Although the frequency of constitutional reaction from intracutaneous therapy is not great, it is greater than from subcutaneous therapy. Phillips reports one systemic reaction for every 125 injections.

There is less discomfort from subcutaneous therapy. Phillips finds that best results are obtained when a pronounced local reaction occurs. I usually see equally good results from subcutaneous therapy with practically no local reaction.

He finds that permanent blemishes are rarely seen although bronzed discolorations fading after a week or so are frequent. The few permanent scars in his experience were due to tissue destruction by scratching, or followed the administration of glycerin extract intracutaneously. Undiluted glycerin extract should not be used intracutaneously. He also found that adrenalin given with the intracutaneous extract tended toward permanent blemishes. Adrenalin and ephedrin under these circumstances favor skin necrosis.

Perhaps the greatest drawback to intracutaneous therapy is the narrow margin of safety. According to Phillips the difference between an ineffective dose and one that oversteps the patient's tolerance is not great. Therefore, treatment must be given with some caution. I have to date seen two mild systemic reactions following small subcutaneous coseasonal doses. This occurred over two hours after the injection, as a generalized urticaria.

In intracutaneous coseasonal treatment Phillips starts with a dose of 0.02 cc. in 1:5,000 solution. Glycerin extract is not used. The dose is increased daily as tolerance permits until the local reaction is at its height some three or four hours after the injection, and is about the size of the patient's palm. Some swelling should remain for twenty-four hours. Sometimes the dose may be doubled each time, at other times the increase is made by only one-fourth or one-half. Some patients stand no increase at all. The succeeding dose is not given until the local reaction has subsided.

If more than 0.17 cc. is to be injected, it should be divided into two wheals. The tougher, less vascular skin of the outer surface of the arm or the extensor region of the forearm is preferred. Previously used sites are avoided. Phillips states that relief is proportionate not so much to the quantity of pollen extract injected as to the extent and vigor of the local reaction. In his experience the average patient required fourteen doses per season. Sometimes only a very few doses were necessary. Those patients with severe local reaction required, as a rule, fewer and smaller dosages. Those with little local reaction were usually not relieved until the dose had been gradually increased, sometimes to as much as one-fourth or one-third of that usually reached in preseasonal treatment.

While Phillips prefers to increase the dose gradually to near the limit of tolerance even though the patient has been relieved early in the course of treatment, we have found it much more satisfactory to maintain the dose steady without increase as soon as the patient is adequately relieved. Subsequent increases are predicated only on a return of symptoms no longer relieved by the established dose for that patient.

Unger reports that he has not been able to duplicate Phillips' 91 per cent in intracutaneous treatment. He has tried both the subcutaneous and intracutaneous methods and does not see any particular difference in the results with the two. Lamson doubts any advantage of the intracutaneous method over the subcutaneous. On the other hand, he believes that the former may be a little safer.

Maurer, on the other hand, points out that there is a very close integration of the blood supply of the skin. He reports the work of Cannon who injected living staphylococci intracutaneously and recovered them in a remarkably short time from the animals' heart blood. He also mentions the work of Opie who demonstrated foreign protein (egg white and horse serum) in the blood stream promptly after intracutaneous injection. The appearance of both of these types of substances in the blood was materially delayed after the animals had been immunized by repeated preliminary injections.

If the basis of successful coseasonal therapy lies in minute dosage and minimal response, Rackemann's early observation should lend weight to the contention that the subcutaneous method is preferable. He observed a constitutional reaction from an endermal dose one-tenth the size of a previous subcutaneous dose which had produced only a mild local reaction.

There are, then, two general methods of coseasonal therapy, subcutaneous and endermal. Both have their advocates and in the hands of competent workers, satisfactory results have been reported with both.

Coseasonal program.—No treatment having been given prior to the onset of symptoms, the patient should first be tested either cutaneously or endermally, to determine roughly the degree of sensitization. If the reaction is average positive, treatment may be started with 1:5,000 dilution. If unusually strong, testing with serial dilutions should be made as described under preseasonal therapy. The proper dilution is determined in the same manner.

Assuming average sensitization the patient is started on daily injections of 0.1 cc. of 1:5,000 dilution. If after the first injection the patient is adequately relieved, this is assumed to be the proper dose and is not increased. Injections are given every day, 0.1 cc. per day. If, after 24 hours the patient is not adequately relieved, the dose is increased by 0.1 cc. each day, until adequate relief

is achieved. Thus, the daily dosage schedule may be 0.1, 0.2, 0.3, 0.4 cc., etc. It rarely is necessary to exceed 1.0 cc. for adequate relief. As soon as a dose is reached at which 75 per cent or more relief is maintained for from 24 to 48 hours, this is assumed to be the proper dose. Thereafter, there is no further increase as long as the patient continues to respond satisfactorily. Injections are given daily for two or three more times. If relief continues, the interval between injections is increased to two days, three days or longer. As soon as practicable the patient is placed on a program of injections twice weekly and the intervals are still further increased, if possible, to once weekly. The program is continued in this way through to termination of the season. Rarely is it practicable to lengthen the interval to more than one week.

If, with a given dose, let us say, 0.6 cc., the patient again develops symptoms, the dose is again increased by 0.1 cc. each day until adequate relief is achieved. As soon as it is achieved, treatment is continued as just described. Occasionally, a patient is adequately relieved for a time with low dosage, following which symptoms recur, and the amount must be stepped up to a new level for relief.

Use of Adrenalin.—Epinephrin 1:1,000 or, better, a mixture of equal parts of epinephrin 1:1,000 and 3 per cent aqueous ephedrin may be given with each injection in dosage of 0.3 cc. This is not essential nor does it improve results. It has the advantage that, if the patient is having symptoms at the time of injection, a single injection of the pollen extract with the adrenalin-ephedrin mixture gives prompt relief. If the patient is not having symptoms at the time of treatment, there is no need for the adrenalin-ephedrin mixture.

Combined preseasonal and coseasonal therapy.—The possibility of coseasonal treatment aids in preseasonal therapy. If an adequate preseasonal top dose has been reached, one may confidently expect that 90 per cent of patients will experience 75 per cent or more of relief from symptoms. This leaves 10 per cent or more who are not adequately relieved. Prior to 1922 nothing more could be offered to this small group. Now they may be treated as coseasonal cases, with the expectation of as much relief as, or more than, that of previously untreated coseasonal cases. The majority treated preseasonally will not require treatment during the season. To those who are not relieved, coseasonal treatment may be administered. It is given entirely irrespective of the degree of partial effectiveness of the preseasonal therapy. Statistically, then, one may anticipate 80 or more per cent relief in the 10 or 15 per cent residue of cases from preseasonal treatment.

The rationale of coseasonal therapy for patients who have had pre-seasonal therapy is based upon the conception that the preseasonal case inadequately or incompletely treated is analogous to a coseasonal case who is only mildly allergic. A mild coseasonal case is analogous to a highly allergic preseasonal case who has been inadequately or incompletely hyposensitized. By virtue of his preseasonal treatment he has been changed from highly sensitized to mildly sensitized.

In the preceding chapter, mention was made of those who report too late for adequate preseasonal therapy but to whom a portion of the prescribed preseasonal schedule might be given, even though the desired top dose cannot be reached. They may be looked upon as rendered less highly allergic, although still allergic, at the onset of the season. Further treatment during the season will be based upon the principles of coseasonal therapy.

Directions for Coseasonal Pollen Treatment

If it is too late to start preseasonal treatment (less than six weeks before hay fever is due), don't start treatment until symptoms (asthma or hay fever) begin. Don't pay any attention to a few sneezes, but if symptoms begin and last more than six or eight hours, then is the time to start treatment.

The two medicines used for injection are a very weak dilution of the pollen extract (1:5,000 concentration), and the regular adrenalin solution (1:1,000); 0.3 cc. of 1:1,000 adrenalin (five minims) is used with each injection of the pollen extract. The *adrenalin* solution is drawn up into the syringe *first*, and then the extract is drawn up. This promotes more accurate measuring of the pollen extract. While the dose of the extract may vary, the dose of adrenalin is always the same (0.3 cc.).

On the first day of symptoms as described above, give 0.1 cc. of the 1:5,000 pollen extract with 0.3 cc. of adrenalin. Just this single dose may give relief for several days. If so, don't give another injection until symptoms return. Then give the same dose (0.1 cc.) of the extract.

If there is no relief after 0.1 cc. of the extract or if relief is not complete, give 0.1 cc. each day for two or three days. This may give relief, in which case leave it off until symptoms return. But if after two injections of 0.1 cc. each day the patient is not relieved, then start increasing the dose by 0.1 cc. each day. The dosage therefore may run somewhat as follows—0.1 cc., 0.1 cc., 0.2 cc., 0.3 cc., 0.4 cc., 0.5 cc. It is rarely necessary to go higher than 1.0 cc. to obtain entirely satisfactory relief.

If, somewhere in this schedule (let us say at 0.3 cc., for example), relief is obtained, remember this dose since it is the proper dose for this particular patient. After this relief is obtained, leave off treatment until symptoms return and then give again that dose which did give good results (such as 0.3 cc.) and repeat daily as long as symptoms persist.

Some persons, unusually sensitive to adrenalin, get some palpitation from 0.3 cc. In this case it will be satisfactory to use 0.2 cc. Remember that the adrenalin (or adrenalin-ephedrin mixture) may be given with each of the injections discussed above.

For further relief if necessary, the following prescription for eye drops, which may be taken any time they are needed (as often as every half hour if necessary), does very nicely.

Adrenalin 1:1,000	4 cc.
Boric acid, sat. sol.	12 cc.

The best nasal spray is a cocaine and ephedrin spray as follows: Ephedrin, 3 per cent aqueous solution, cocaine hydrochloride 2 per cent aqueous, equal parts to make 60 cc. The cocaine may be omitted if desired.

Three-eighths grain ephedrin capsules or "ephedrin with amytal" capsules may be taken every three or four hours if necessary. The ephedrin nasal jellies in soft metal tubes are very handy. As a rule, however, none of these medications are necessary, adequate relief being obtained with the desensitization injections only.

Rinkel's method.—Dilutions of testing extracts are made using normal saline containing 0.4 per cent phenol. Dilutions are made every two weeks to avoid deterioration. The dilutions used are shown in Table XLIV.

TABLE XLIV. DILUTION

DILUTION	DESIGNATION	DILUTION OF ANTIGEN
Concentrate	10	1:20
1:5	9	1:100
1:25	8	1:500
1:125	7	1:2,500
1:625	6	1:12,500
1:3,125	5	1:62,500
1:15,625	4	1:312,500
1:78,125	3	1:1,562,500
1:390,625	2	1:7,812,500
1:1,953,125	1	1:39,062,500
1:9,765,625	0	1:200,000,000
1:48,828,125	00	1:1,000,000,000
1:244,140,625	000	1:5,000,000,000

Testing is done using the suspected pollens and any others which are in the air at that time. Begin with the No. 1 solution and put in 0.01 cc. intracutaneously. The reactions are read in ten minutes, and then No. 2 solution is used and read in ten minutes. This process is continued, increasing the concentration each time until a reaction showing a wheal of 7 mm. and erythema of approximately 25 mm. is reached. This is termed the end point of erythema, and tests are not made with more concentrated extracts of that antigen. It is necessary that the wheal from the injection should measure 4 mm. in diameter immediately after the injection. When the wheal is erythematous instead of pale this is not the end point.

The first dose of treatment is fifteen times the erythema dose. For example, if the end point of erythema is with Solution No. 4, treatment may be given with 0.15 cc. of No. 4. It would be safer, however, to use 0.75 cc. of No. 3 since a larger volume of a weaker solution is absorbed more slowly and diminishes the risk of systemic reaction.

If the first dose did not give relief the next dose is given after twenty-four hours. If it did relieve, the second dose is withheld until the symptoms recur. Then use a multiple of 25 times for the primary pollen and fifteen times the erythema dose of any secondary pollens.

The third dose is given twenty-four hours later if no relief was had and withheld, if relief occurs, until symptoms reappear. The dose is thirty-five times the erythema dose. Subsequent doses may be 50, 75, 100, and 150 multiples of the erythema dose. In every instance it is to be remembered that a dose is not to be repeated until the relief from the preceding dose is exhausted. No dose is to be increased beyond the amount required to secure relief for four to six days. Usually the fourth dose is given not sooner than three days after the third, and the fifth dose is similarly spaced after the fourth if relief is not secured. Overdosage is to be avoided. Rinkel has not found doses larger than multiples 75 to 100 times the erythema dose necessary for relief. As long as relief is satisfactory for a given period of time the dose is not increased. As a rule, the more sensitive, the patient, the smaller must be the dose and the shorter may be the period of relief. The less sensitive the patient the larger may be the dose and the longer the relief.

This method is distinguished by the method of determining the initial dose, and adherence to small doses. It requires time, accuracy of technic, and careful observance of details. Those who have had experience with the method agree that results are excellent.

CHAPTER LII

PERENNIAL POLLEN THERAPY

In 1920 Walker wrote, "If pollen cases were treated as long and as consistently as the animal hair protein cases, many patients would possibly be free from symptoms entirely, for years, if not throughout life." Stewart wrote (1926) that she was treating cases of pollen sensitization throughout the year; with injections twice monthly. However, the first two comprehensive reports on perennial treatment were those by Aaron Brown and by Vander Veer, Cooke and Spain (1927). The latter wrote that, after having observed satisfactory results from continuous horse dander desensitization, they applied the method in seasonal pollinosis, with equally good results. Brown described a program for perennial treatment which has been the basis for subsequent work in this line. His observations of good results were confirmed by Figley (1930), by Vaughan (1931), and by Thommen (1931). Perennial treatment has since become an accepted procedure.

Kahn (1927) independently described good results from perennial treatment of patients who are exposed to pollen in Texas practically throughout the year. He believes that best results are obtained when treatment is given in sufficiently high dose and at frequent enough intervals to eliminate entirely local reactions following injections. Injections once weekly achieved his purpose. He therefore recommended weekly injections throughout the year. At that time he also suggested that his perennial procedure might be used as maintenance therapy in cases with short pollen season, the maintenance dose being reduced in the symptom-free interval to from one-fourth to one-tenth the maximum dose.

Difficulties and reactions.—Although perennial treatment early in its development, following the method of Brown, was accompanied by an increased frequency of systemic or constitutional reactions, this difficulty has been obviated in great measure. Brown's recommended interval between injections was one month. This is a long time and in some cases undoubtedly allows for some loss in hyposensitization. He used extracts which did not contain glycerin and which therefore deteriorated rather rapidly. As a consequence when change was made to a newer, fresh extract, actually stronger than the old extract, reactions were likely to occur.

In 1932 he reported about one constitutional reaction in every 200 injections. Figley (1930) reported one general reaction in 200 injections; in 1933, a still smaller proportion following the addition of epinephrin to each injection. Unger (1932) observed 34 general reactions in 18 patients following preseasonal treatment, as compared with three reactions in the same number from perennial treatment. Peshkin observed (1936) one general reaction to every 333 preseasonal injections based upon a total of 9,327 injections, as compared with one in every 105 perennial injections based upon a total of 3,668 injections. This was in adults. In children the proportion was more nearly the same; preseasonally one in 777 injections based on a total of 6,222 injections; perennially one in 827 injections, based on a total of 3,309. Combining adults and children he observed one general reaction in every 431

preseasonal injections as compared with one in 178 perennial. He concluded that with the perennial method general reactions occurred about two and a half times more frequently than with preseasonal.

There is one difficulty in making comparisons of these observations: the definition of a systemic or general reaction. Peshkin defines a constitutional reaction occurring during the course of pollen treatment as "any unfavorable symptom or symptoms following an injection of pollen antigen. The symptoms may be mild or so negligible as to escape notice or they may be alarmingly severe. A general reaction may prove fatal. A general reaction may occur within a few minutes to even two days after an injection and may be manifested by only slight sneezing or a transient headache or violent asthma or dermatosis." It seems probable that many investigators would not consider the term as inclusive.

There are several features in the rationale of perennial therapy.

1. **Possible superiority.**—To be recommended as superior or preferable to preseasonal or coseasonal therapy, the procedure must give better results, a higher percentage of relief. Vander Veer, Cooke, and Spain reported satisfactory results in 85 per cent of their preseasonal cases, 95 per cent in the perennial series. Vaughan reported 71 per cent satisfactory in the preseasonal series, 100 per cent in the perennial series. Unger reported 76 per cent satisfactory preseasonally, 95 per cent perennially. Colmes reported 88 per cent satisfactory preseasonally, 91 per cent perennially.

On the other hand, Thommen observed no particular advantage as far as results are concerned. In two patients the results were distinctly less favorable. They had previously received preseasonal treatment for 7 and 6 years respectively, with most satisfactory results. These patients experienced constitutional reactions for the first time, during preseasonal treatment.

Peshkin has made a comprehensive study of 100 patients treated perennially who had been satisfactorily relieved in previous years with preseasonal treatment only. He observed failure of relief in 11.6 per cent of those treated perennially as contrasted with 5.1 per cent of those treated preseasonally. Some patients who had done well under preseasonal treatment did not do as well when later subjected to perennial. The reverse was also true in certain cases although less frequently so.

More recently, Spain and Fuchs (1937) reviewed comparative results from preseasonal and perennial treatment in 950 adult patients, finding that 73.4 per cent of preseasonal cases experienced effective relief as contrasted with 94.2 per cent under perennial treatment. Constitutional reactions occurred more frequently in the preseasonal group.

We must conclude that while the majority believe that results are somewhat better following perennial treatment, other investigators have not found this the case. Loveless believes that results are much better with preseasonal treatment one season and a few "booster" injections just prior to the following season.

2. **Permanent cure.**—The suggestion was made when this method was first presented, that it offered greatest promise of permanent cure. The possibility existed that continuous or frequently repeated exposure to the allergen might ultimately produce a permanent tolerance so that after several years of perennial treatment, desensitization could be discontinued indefinitely.

I cannot say that I have seen an undoubted permanent cure even after four years of perennial desensitization. Often after such a course the patient

will go three or four years or longer before requiring further treatment. Sometimes coseasonal treatment must be given even the first year after discontinuance. However, Brown's first perennial case to whom he gave treatment steadily from 1920 to 1925 had no treatment and no return of symptoms in the ensuing ten years. Therefore, the possibility still exists. It may be that treatment should be continued longer than has usually been done.

It should be borne in mind that some persons recover spontaneously. I have seen several with histories of having had hay fever in one or another season who still gave positive reactions to the appropriate pollen but who had been symptom free for two or more years without treatment. Walker (1932) found that 20 per cent of his cases treated only preseasonally were eventually relieved so that they required no further treatment of any sort. Rackemann (1929) reported similar results in 6.3 per cent of preseasonal ragweed cases; 7 per cent of timothy pollinosis treated preseasonally. Thommen (1931) reported 6.8 per cent permanently relieved following several courses of pre-seasonal therapy.

We must conclude that the possibility of eventual permanent cure following perennial treatment has not been proved. It would seem to be the current consensus that there are no more permanent cures following perennial than those following preseasonal therapy.

3. Convenience.—With the perennial method treatment may be started at any time of the year and there is no such urgency with regard to reaching an adequate top preseasonal dose as when preseasonal treatment is started rather late. Intervals between injections may be lengthened. It is often more convenient for the patient to come to the office less often and over a longer period of time. It is distinctly more convenient for the physician, who may distribute his work through the year, avoiding the heavy load just prior to the season. The occasional extremely reactive patient who must start with a higher dilution than 1:5,000 or 20 Noon-Coca Units has more time in which to reach the desired top dose.

Procedure.—Unfortunately, many allergists have therapeutic modifications of their own, so that it is often difficult to compare the results of different observers. Clarke and Friedman reported distinctly inferior results with coseasonal therapy. On discussion it developed that their coseasonal procedure did not involve radical dosage reduction from that reached just prior to the season. Their results, therefore, obviously could not be compared with the results from coseasonal treatment as described in the preceding chapter. In the same way, in perennial therapy, different observers use variously prepared extracts, treat at varying intervals, and recommend several different maintenance doses.

Irritative reaction.—The writer has not had occasion to compile a comparison of his results with the three standard methods since his first paper on perennial therapy (1931). However, it is my impression that with the method which I employ there is less tendency toward constitutional reaction, the percentage of patients obtaining relief is slightly greater, and the patient is likely to do better generally throughout the entire year, especially as regards attacks of acute nonallergic coryza. We do see a few, probably not more than one or at most two per cent, of what Peshkin terms "irritative general reaction" in which the patient develops some new or different allergic manifestation outside the pollen season, which seems to be kept active by the repeated injections. In our experience the irritative general reaction mani-

fects itself in the following order of frequency: gastrointestinal symptoms, headache, skin manifestations especially eczema, asthma, pyrexia. Discontinuance of perennial treatment is followed by disappearance of the reaction. In such instances no further attempt is made at perennial therapy, the patient being directed to report for preseasonal or coseasonal treatment. It should be noted that the irritative general reaction may occur, and probably occurs as frequently, in the course of preseasonal therapy. In such cases it is especially important to search for other allergenic factors such as foods or non-pollen inhalants. Often control of the latter will prevent the irritative general reaction. Metabolic disturbance such as a subthyroid state is sometimes discovered.

Routine.—The author's customary routine is as follows. Treatment is initiated at any time prior to the pollen season. The allergenic pollen having been determined, injections are given at weekly intervals according to the procedure described in preseasonal therapy. After reaching the higher concentration (1:50), instead of progressing on to the top preseasonal dose, a maintenance dose, approximately one-fifth of the former is held steady until shortly before onset of the season. As soon as the maintenance dose is reached (usually 0.2 cc. of 1:50 or 4,000 Noon-Coca Units) the frequency is reduced to biweekly or semimonthly. Four or five weeks prior to the season the patient again reports once weekly, during which time the dose is successively increased by 4,000 units, to reach a top dose of 20,000 at the season. As a rule, only one dose of 20,000 units is given. Immediately after the onset of pollination, the dose is again dropped to maintenance, 4,000 units twice monthly. This is continued throughout the season and on through the year, until the time arrives for again stepping up to top dose, four to five weeks prior to the next succeeding season.

Under no circumstance is the top dose to be continued into the season. I find this error frequently committed. It often results in constitutional reactions. The top or protective dose is designed to enable the patient to tolerate the largest exposure which he is expected to receive normally through the respiratory tract during the season. If the top dose is continued, the patient must tolerate on days of treatment not only the amount of allergen which he is inhaling but also the largest amount that his tissues have learned artificially to tolerate. Obviously the summation effect may be expected to exceed tolerance and precipitate symptoms.

When treatment is discontinued there is a gradual return to the sensitized state. Complete return may occur in three or four months. Even after one month, enough tolerance may be lost to produce symptoms following reinjection of the same top dose. A two-week interval is safe for the maintenance of any dose. Presumably, there has been some loss in tolerance, but not enough to cause symptoms after the subsequent injection.

If, therefore, perennial treatment is continued, injections must be given through the pollen season. They should be given at two-week intervals at a decided drop from the "top dose," to the "maintenance dose." Employing this program we have observed no untoward reactions.

Preparation of the extract is most important. Constitutional reactions following perennial therapy have been reported for the most part by allergists who have given treatments at monthly intervals with extracts not containing glycerin. Glycerin appears to be the most effective preservative so far employed. Apparently, its only disadvantage is that it is irritative and causes

some pain when given subcutaneously. Patients manifest hyperesthesia to it in varying degrees. Rarely it is so painful that one must change to another extract. Occasionally, a patient will react to glycerin extract with subcutaneous inflammatory response, swelling, local heat, redness, and tenderness which does not occur in the same patient following injections of an extract not containing glycerin. In such cases glycerin extracts cannot be used satisfactorily. Those who have used dextrose extracts (Unger) report its keeping qualities equal to glycerin.

Piness has found that glycerin extracts retain potency almost undiminished, even at room temperature, sometimes as long as ten years. The advantage of an extract which does not lose potency is obvious. With one which does lose it rapidly, a change from an old extract to a newer fresher one of presumably the same dose involves actually giving a decidedly larger dose and may cause reaction.

Glycerin extracts.—Glycerinated extracts have been popular with many allergists since they were introduced in 1922 by Clock. His original extract contained two-thirds glycerin, one-third saturated aqueous sodium chloride.

Most glycerin extracts recommended since have been but variations of the original Clock solution. Since in many cases the variation has been slight, and the Clock solution has been the original basis, it seems supererogatory to designate each new solution, as has been done, by the name of the man proposing it. The general principle of the variations has been that the high glycerin and salt content is irritating and causes pain of varying degree. It has been found that the proportion of glycerin may be reduced to as low as 45 per cent without impairing extracting ability or preservative activity. It has been found that the strength of sodium chloride may be materially reduced, even to physiologic saline, so that the aqueous moiety may consist of plain physiologic saline or the alkaline extracting fluid described by Coea. With these changes, pain caused by injection has been so far reduced as to be negligible in most cases.

Black* suggests the addition of 1 per cent Butyn or novocaine to glycerin extracts to counteract the pain. The proper dose of the glycerin extract is drawn up in the syringe, after which 0.2 cc. of butyn solution is also drawn up. Although butyn is a recognized cause of contact dermatitis on the skin and mucous membranes, Black has seen no evidence of reaction to subcutaneous injections.

Aaron Brown has recently adopted glycerin extracts in perennial treatment. He lists the advantages as follows: They are self sterilizing ; stable, maintaining full activity for years; may be made up in large quantities at a time; may be used without deterioration during the course of perennial therapy; may be diluted for intracutaneous testing; and are safer for treatment, being absorbed less rapidly. Constitutional reactions occur in about the same frequency but are less severe. Brown, who prior to 1932 had not used glycerin extracts, reported that his results in 1932 were superior to those of previous years.

Dextrose extracts.—Unger and Moore have attempted to improve the extracting power and to prolong potency by the use of 5 per cent dextrose. They find that dextrose extract remains potent for at least 30 months. Clinical results with these two types of extracts were about equal. Constitutional reactions occurred in about the same proportion; 1.03 per cent with glycerosaline

*Black, J. Harvey, Dallas, Texas. In the International Correspondence Club of Allergy

and 1.2 per cent with dextrose. They claim two advantages for the dextrose extract; that it may be used for intracutaneous testing, and that it is easier to handle, being more easily drawn through the needle.

Rappaport,* however, states that ragweed pollen solutions in 5 per cent glucose and 0.5 per cent phenol menstruum deteriorated 35 to 50 per cent in about three months.

Other extracts.—When, for some reason, extract not preserved with glycerin or glucose must be used in perennial therapy and the possibility of rather rapid deterioration exists, change may be made from an old extract to a new fresh one by the method outlined by Brown. During the changeover which is accomplished in three or four injections, one gives a mixture of the old and new. The first injection may contain three-fourths old, one-fourth new; the second equal parts; the third one-fourth old, three-fourths new; while the fourth injection will be entirely the new extract. During the changeover, injections should be given at no longer than weekly intervals.

Pick-up program.—Occasionally a patient cannot return at one of the appointed two-week intervals. If the interval is much longer, the next dose should be reduced. The writer has found the following schedule of reduction safe provided the patient has not previously shown a tendency toward systemic or constitutional reaction.

TABLE XLV.—SAFE PICK-UP DOSE WHEN THE TIME SINCE LAST PREVIOUS INJECTION HAS EXCEEDED TWO WEEKS

Assuming a Previous Maintenance Dosage of 4,000 Units or 0.2 cc. of 1:50 Extract		
INTERVAL	UNITS	DOSAGE
2 weeks	4,000	0.2 cc. of 1: 50
3 weeks	4,000	0.2 cc. of 1: 50
4 weeks	2,000	0.1 cc. of 1: 50
6 weeks	1,000	0.05 cc. of 1: 50
8 weeks	400	0.2 cc. of 1:500
10 weeks	100	0.05 cc. of 1:500

The pick-up is completed with weekly injections with the usual series of increases, until the maintenance dose is again reached. Treatment is then given biweekly as usual. If the interval has exceeded ten weeks, it is safest to start again with 20 units.

Method of Transfer to a Fresh Extract When Not Using Glycerin Preparations

It is in perennial treatment that accurate standardization by total nitrogen or protein nitrogen content finds greatest clinical usefulness. Those who prefer to give perennial injections only once monthly find that a certain proportion of patients experience mild constitutional reactions from time to time, especially if they try to stay at maximum dosage. An extract, once made up, steadily but gradually deteriorates. A simple saline extract, preserved under ideal precautions, loses about 50 per cent of its activity in 12 months. If after a number of months the patient is suddenly changed from this partially deteriorated extract to a new one (made up to the same strength and theoretically the same, but actually twice as strong, due to its freshness), a severe constitutional re-

*Rappaport, Ben Z., Chicago, Ill. In the International Correspondence Club of Allergy

action might ensue. However, Cooke and his coworkers have found that even though the protein content has diminished by 50 per cent, that which remains is allergenically as potent as it was originally.

To maintain the same dosage with this type of extract, one would have to gradually increase the size of the dose until at the end of a year the patient is receiving twice the amount of the same extract as he had received the year before. Then, the actual dose of protein would be the same (not increased), and the volume would have been doubled.

Since extracts made up by different methods deteriorate at different speeds, and since extracts are not always kept under ideal environmental conditions, this simple theoretical program is not as a rule altogether practical.

A simpler and more rational procedure and at the same time safer, would be to make a protein nitrogen determination on the old extract just before it has been discarded, compare this with the protein nitrogen content of the next extract, and give the first injection of the new extract at a reduced dosage, containing the same number of protein units as is represented in the last dose given of the old extract. From this point the dosage can then be worked up as desired.

Cooke, Vander Veer and Barnard have worked out a plan of change from old extract to new extract which in their experience works satisfactorily, as follows: In the relatively insensitive case without tendency to general reaction the change from old to new extract may be made completely at one time. In the moderately reactive case the new extract is given in one-half or three-quarters the size of the last dose of the old extract. Thirty minutes later the balance is given. By "dose" we mean the volume of a given concentration as indicated on the label, ignoring the fact that there has undoubtedly been some deterioration. In the very reactive case one-half of the last dose is given. A week later three-quarters of the dose is given and after another week the full dose is administered. This program, while not as accurate as that mentioned above (actually determining the protein nitrogen of the old extract and of the new, and giving accurate dosage based thereon), nevertheless provides a procedure which the authors believe safe for those physicians who are not in a position to make nitrogen determinations.

CHAPTER LIII

DISCUSSION OF POLLEN THERAPY

There are, as we have seen, three general methods of treatment. Are there any special indications for the preferential use of one or another under given circumstances? Each has its field of usefulness. In some instances two or more of the methods may be used in the same case. The appropriate plan of specific treatment to be selected under given circumstances can be most lucidly described in a discussion of the following case problems.

Preseasonal satisfactory.—

1. *Preseasonal treatment gives satisfactory relief, the patient requiring no further injections during the season.*

This appears to have been a very satisfactory method in this case and there is no reason to change. The patient is discharged with directions to return preseasonally the following year. There is no need to continue injections during the season. We have seen that there is gradual loss of tolerance and one might argue that with a six- or eight-week season the patient's tolerance might fall toward the end to such an extent that symptoms would ensue. However, this does not occur. During the first half of any pollen season a patient is more reactive to a given atmospheric concentration of the pollen than he is during the second half. This is shown in the chart by Waldbott and Ascher. The process may be looked upon as akin to that of acclimatization. In the latter part of the season a larger atmospheric dose must be received before symptoms become manifest. Another way of expressing the phenomenon is that continued exposure through inhalation keeps up or even improves the patient's tolerance.

If perennial treatment is not to follow, there is no need for further injections. If, on the other hand, perennial treatment is given, it is safest to continue the injections at reduced or "maintenance dose" through the season. This is sufficiently below the top dose to avoid reaction.

Preseasonal unsatisfactory.—

2. *The patient has reported for treatment two months prior to onset of the season. He is given preseasonal therapy, the proper top dose having been reached just prior to pollination. However, he does not receive adequate relief. Preseasonal therapy in his case has been unsatisfactory.*

Treatment may be continued coseasonally. Injections are given daily or even twice daily, but the dose is reduced to 10 or 20 pollen units. Coseasonal treatment is given in the regular schedule just as though the patient had had no preseasonal treatment. Two patients who have had no preseasonal therapy will start on the same coseasonal program even though one may be much less highly sensitized than the other. We may look upon our problem case as corresponding with the less highly sensitized of the two. He was highly sensitized before starting treatment; treatment made him less so; but he is still having symptoms and should be treated during the season as a mild pollinosis case without previous treatment.

Since preseasonal treatment fails to give adequate relief, it would be appropriate to recommend perennial treatment in the hope of better results the following year. This usually happens.

To go on with perennial treatment.—

3. *Preseasonal treatment has been inadequate. Small dosage coseasonal treatment is being given. The patient will be continued on perennial therapy.*

Here we are faced with the problem of daily injections of 1:5,000 concentration and, at the same time, biweekly injections of 1:50. This appears irrational. Both series are given, but for entirely different purposes. The biweekly injections are for maintenance, to prevent tolerance from falling beyond a certain limit. Daily injections are for relief of symptoms. Thus one may be giving 1:5,000 injections on successive days, then an injection of 0.2 cc. of 1:50, and, if the patient is still having symptoms, return to 1:5,000 the following day. The two processes are continued entirely independently.

Coseasonal satisfactory.—

4. *The patient seeks treatment for the first time during the season. Coseasonal therapy is given, with a total of possibly from 6 to 12 injections. Results are satisfactory.*

Relief was obtained with the least inconvenience to the patient and the smallest number of doses. The probability is that results will be comparable on succeeding years. The patient is discharged with directions not to return until symptoms recur a year hence.

Insufficient time for preseasonal.—

5. *The patient reports for treatment two weeks prior to the season, too late to achieve adequate preseasonal desensitization.*

He may be told that it is too late, that it would be as well for him to wait until he develops symptoms, when he will be given coseasonal treatment. Or, he may be given a short and inadequate preseasonal course with injections twice weekly, no attempt being made to reach the proper top dose. He should understand that he will probably also need coseasonal treatment; that the short preseasonal treatment will, theoretically at least, make a more highly reactive individual somewhat less so and consequently more easily relieved with coseasonal treatment.

Perennial treatment.—

6. *The patient has fall hay fever but is always away from home during the summer, finding it difficult to procure preseasonal treatment.*

Coseasonal therapy may appropriately be tried or he may be placed on perennial treatment. This reduces to a minimum the number of injections given during the summer vacation.

Continuation with perennial.—

7. *Patient first reports for treatment during the season with the statement that he has always intended to take preseasonal treatment but never gets around to it.*

He will be given coseasonal therapy followed without an interval by perennial treatment, unless the coseasonal program alone proves satisfactory. As soon as he has been relieved coseasonally, he is directed to return at weekly intervals. The coseasonal maintenance dose is continued. When the season is

over, hyposensitization is given with weekly injections, according to the pre-seasonal schedule, until the maintenance dose is reached. Thereafter, the frequency is reduced to twice monthly and continued through the year until about one month prior to the next season. During this last month the maintenance dose is rapidly raised to the top dose with weekly injections. Assuming a maintenance dose of 4,000 units or 0.2 cc. of 1:50, successive weekly injections just prior to the next season will be 0.4 cc., 0.6 cc., 0.8 cc., 1 cc. When the dose is being increased it is safer to employ weekly or semiweekly intervals. When it is being kept steady at any level a biweekly interval is safe, except with the very rare extremely allergic case.

Occasionally a surprisingly small number of doses coseasonally will give relief. I have one patient who quite regularly receives 90 per cent relief following one injection given once each year, just after the onset of symptoms. Rarely he requires three or four.

Multiple Pollen Problems

Trees, grasses and weeds.—

8. *The patient reacts to five different grass pollens. Should a single pollen such as timothy, Bermuda grass, or red top be used in treatment as a representative of the entire group or should he be treated with extracts of all of those pollens to which he reacted? If the latter, should the final top dose be, let us say, 20,000 units of each of the pollens or 20,000 of all five together, that is 4,000 of each?*

Evidence of family specificity.—As pollen studies have progressed it became apparent that there is a clearly recognizable tendency toward crossed reactions among pollens from plants belonging to the same family or genus. Scheppegegrell (1932), testing grass allergies with over 100 varieties of grass pollen, observed positive reactions to all, as contrasted with simultaneous negative reactions to other pollens. He interpreted this as a family, group or crossed reaction. He observed clearly recognizable variations in the intensity of the reaction to different grass pollens.

Thommen (1931) reached similar conclusions in a study of 30 patients tested with the pollens of 81 species, representing 50 genera. Among Americans atopic to grass he observed positive reactions to the pollen of a grass indigenous to Spain to which they had never been exposed.

Cooke and Vander Veer found that in New York City grass sensitization was almost invariably associated with allergy to timothy. They concluded that there is a crossed reaction among the grasses and that timothy desensitization adequately protects against other grasses. Freeman, Goodale and others agree with these observations. Chobot has shown that timothy pollen extract desensitizes against Bermuda grass and vice versa.

Similar observations have been made with the Compositae. Walker (1921) found that from 21 to 50 per cent of his ragweed cases give simultaneously positive reactions to goldenrod, daisy, golden glow and sunflower. Vaughan and Crockett found that in Virginia one out of every 3 ragweed allergies is also allergic to goldenrod.

Cooke, Vander Veer and Spain, Aaron Brown, and Spain and Hopkins, on direct skin testing found simultaneous positive reactions to giant and short ragweed, with no recognizable quantitative difference.

Evidence indicating the biologic identity of the reagins of giant and short ragweed has been presented in passive transfer experiments by Coea and Grove, Stull, Cooke and Chobot, while Walzer and Grove reached similar conclusions using the Dale uterine strip technic.

Bernton reported an experience analogous to that of Thommen with an exotic pollen. He found a positive cutaneous reaction to tithona, a South American composite, in a ragweed allergic.

Sellers and Adamson concluded from passive transfer studies that the antigenic properties of the amaranths are identical and that those of the chenopods are very similar but not identical. They concluded that desensitization with any member of the first group will control symptoms due to other members of the two classes of plants.

The accumulated evidence just reviewed appeared to justify the conclusion that adequate hyposensitization could be accomplished clinically by the use of but one member of any biologic group to which an individual is allergic. This materially simplifies the problem of the commercial preparation of pollen extracts and, as we shall see, probably accounts in part for the not infrequently observed failure of commercial extracts to achieve desired results.

Evidence of species specificity.—We have stated above that evidence of crossed pollen reaction was usually observed, but that a quantitative variation was often recognized. Watson and Kibler (1922) found that a large number of their patients allergic to Bermuda grass did not show positive skin reactions to timothy and questioned the exclusive use of the timothy pollen extract in treatment. Lamson and Miller, also Piness and Miller reached similar conclusions. Coea and Grove found that timothy desensitizes areas passively sensitized to orchard grass but that orchard grass does not completely desensitize against timothy. They concluded that some of the atopens of timothy are not present in orchard grass.

Rackemann and Wagner, working with timothy, orchard grass and redtop, have reported conclusions which would indicate that timothy is not a universal desensitizer for the grass family in the New England States. They state, "Crossed reactions between different grasses and between different trees are by no means unusual. Treatment of a passively sensitized site with either timothy, orchard grass, or redtop results in most instances in simultaneous desensitization with the other two grasses but the important fact is that no one of the three grasses always and invariably produces desensitization to the other two. Observation of patients in the clinic indicates that whereas most of our patients with early hay fever show positive skin reactions to all of the grass pollens at the same time and in about the same degree, there are occasional instances of single sensitivity and in other instances reactions to only two of several grasses. Furthermore, our results of treatment with a single grass pollen extract have not been as satisfactory as the results in other cases in which at least two pollen extracts were used."

Bernton, also Rappaport and Johnson, found differences in the intensity of skin reactions to extracts of giant and short ragweed. This has been my own experience. Occasionally we have seen positive reaction to short ragweed with a completely negative reaction to giant, confirmed on retesting, and vice versa.

Moore, Cromwell and Moore, Armstrong and Harrison, Cromwell and Moore, and Cooke, Stull, Hebard and Barnard, using various methods of study such as passive transfer, reagin exhaustion, rabbit anti-ragweed serum, the

trypan blue reaction in sensitized rabbits, reagin neutralization, and therapeutic studies, all reached the conclusion that the allergens of giant and short ragweed are not identical despite the commonly observed crossed positive skin reaction.

The evidence would indicate that although biologically related pollens show common antigenic activities, these are not completely identical for all pollens, each pollen possessing a reactive capacity of its own which may differ from that of other members of the same family. We may speak of group or family positive reactions and species positive reactions.

As a matter of fact, this is what one would anticipate in view of past similar observations with other antigens. Wells, also Hektoen and Cole, observed five antigenic components of hen's eggs some of which were identical with those of duck eggs, others not. It is well known that the lactalbumin fraction of milk tends to be species-specific while the casein fraction is usually antigenically similar for all milks. Wells found an identical antigen in wheat and rye, a closely related one in barley, and at the same time species-specific antigens in all three. Vaughan, Baldwin, Withers have observed group sensitizations among the common foods and, at other times, individual sensitization within the members of the groups. Talbott and Freeman, Walzer and Bowman have demonstrated similar group and individual reactivities among horse, donkey and zebra allergens. A similar situation has been shown to exist in the lower forms of life such as amebae and bacteria. Among the bacteria, group reactions in the typhoid-paratyphoid group, and the specific carbohydrate and protein reactions in the pneumococcus group are familiar examples.

Clinical application.—For the last fifteen years it has been my custom to test with several different species of the weed and grass families rather than with one or a few representative members. In 1931 Vaughan reported on the relative frequency of positive skin reactions. He found that while there was a definite tendency toward group reaction, this was not constant since some pollens reacted positively much more frequently than other members of the same family. Among the grasses, those which are generally recognized as being most frequently causative of pollinosis gave the most frequent positive reactions, but even here there was distinct variation. Grasses which are not widely distributed through the southeastern states and whose pollen is therefore not abundant, and pollen from plants which shed little, such as wheat, rye, crab grass and barnyard grass, produce few positive skin reactions. Similar observations were made among the composites, the chenopods and the amaranths.

The writer's findings.—Grubb and Vaughan (1938) found in a series of 218 grass allergies tested with 10 different grass pollens that there was no one grass which caused positive reactions in all. Redtop did so most frequently, being positive in 65.6 per cent. About 25 per cent of the entire series reacted to all ten grasses. Although there was definite evidence of group specificity, there were 37, or 17 per cent, who were species-specific, reacting to only one species of grass pollen. These species-specific reactions occurred, in one case or another, to all ten of the species tested. Fifty-eight per cent cross reacted with two or more grasses but not with all.

In 17 per cent sensitization was completely species-specific and there was no evidence of group reaction. Furthermore, this condition existed with every grass used for testing and is therefore probably true for all hay fever grasses. Obviously no one grass may be used as a representative of the family for routine testing. If we were to take redtop as the most promising single grass for

testing, we would find that approximately 15 per cent of grass allergies would react to some other single grass, with no multiple reactions. Furthermore, of the single and multiple reacting allergies, only approximately 66 per cent would react to redtop. If redtop alone were used for testing, one-third of the cases of grass sensitization would be missed. If redtop alone were used in treatment, it would be reasonable to assume that no benefit would be obtained in the 15 per cent allergic only to species-specific allergens other than redtop. The degree of benefit with the remainder would depend upon the relative proportion of group-specific and species-specific allergens.

Grubb and Vaughan reached similar conclusions in their study of sensitization to the Compositae and to the chenopod-amaranth group. While there were many group-specific reactions, there were also species-specific reactions in all of these groups. This was true even with giant and short ragweed. Among 255 ragweed allergies 90.2 per cent reacted to short ragweed, 71.3 per cent to giant ragweed. Nine were reactive to short but not to giant while 5 were reactive to giant but not to short.

It becomes obvious that for best results testing must be done with the individual species among the pollen families, tribes or genera. Similarly, the evidence would indicate that best therapeutic results will be obtained by treating with extracts of all those species to which the individual is actually exposed during the time when he has symptoms.

This last statement must be literally interpreted. Let us say that a patient reacts to sweet vernal grass which pollinates early in the grass season and to redtop and timothy, which pollinate late. He has symptoms only early in the pollen season. Therefore, sweet vernal grass extract alone should relieve symptoms. When symptoms persist throughout the grass season, early and late, all species of grass to which the patient is actually exposed may be incorporated. However, there is no need for incorporating those to which he is *not* exposed even though they are in his vicinity and pollinating at the time. One living in the North, where there is little or no Johnson grass, needs no treatment therewith even if he be skin test positive. Presumably, the positive reaction represents group or family sensitization. This applies to such self-pollinating, nonanemophilous grasses as wheat and crab grass. Not every patient reacting to ragweed and goldenrod needs goldenrod therapy, since there may be no actual exposure. But if there is close exposure, results should be better if goldenrod is added to the treatment material.

What should be the top dose? The writer customarily treats ragweed allergies with a mixture of equal parts of giant and short ragweed extract. The top dose is usually 20,000 units which represents 10,000 of each. The same is true of the grasses. A top dose of 10,000 or 20,000 units is represented by proportionately smaller quantities of as many grasses as are in the treatment material.

When goldenrod must be incorporated with the ragweed, the writer has found that adequate relief is obtained with 20,000 units representing approximately 6,600 units each of giant and short ragweed and goldenrod. In other words, family specificity appears to be the more important but species specificity should be recognized in the selection of appropriate treatment material.

When we are dealing with unrelated pollens such as ragweed and English plantain or ragweed and the grasses, or trees and grasses, the top dose should not represent a composite but should be independent for all unrelated pollens.

TABLE XLVI.—*Gramineae* 218 POSITIVE CASES

	TOTAL	PER CENT	JOHNSON GRASS		CRAB GRASS		REDTOP		SWEET VERNAL GRASS		TIMOTHY		BERMUDA GRASS		ORCHARD GRASS		VELVET GRASS		JUNE GRASS		BROME GRASS	
			NO.	PER CENT	NO.	PER CENT	NO.	PER CENT	NO.	PER CENT	NO.	PER CENT	NO.	PER CENT	NO.	PER CENT	NO.	PER CENT	NO.	PER CENT	NO.	PER CENT
Johnson Grass	97	44.5	(3)		64	65.9	80	82.3	69	71.0	63	64.9	48	49.2	64	65.9	39	40.2	64	65.9	56	57.7
<i>Holcus halepensis</i>	90	41.3	64	71.1	(5)		76	84.4	63	70.0	57	63.3	45	50.0	55	61.1	39	43.3	59	65.5	55	61.1
Crab Grass	143	65.6	80	55.2	76	53.1	(5)		97	67.8	82	57.3	62	43.3	90	62.9	50	34.9	93	65.0	74	51.7
<i>Pennisetum d. chlorocephalum</i>	119	54.6	69	57.1	63	54.6	97	81.5	(4)		75	63.0	54	45.3	77	64.7	50	42.0	77	64.7	63	54.6
Redtop	99	45.4	63	63.6	57	57.5	82	81.8	75	75.7	(7)		48	48.3	69	69.6	41	41.4	69	69.6	58	58.4
<i>Lycopodium alba</i>	76	35.1	48	63.1	45	59.2	62	81.8	54	71.0	48	63.1	(4)		55	72.3	29	38.1	50	65.7	46	60.5
Sweet Vernal	105	48.1	64	60.9	55	52.3	90	85.7	77	73.3	69	65.7	55	52.3	(2)		45	43.3	78	74.2	67	63.8
<i>Lathyrus odoratus</i>	57	26.1	39	68.4	39	68.4	50	87.6	50	87.6	41	71.9	29	50.8	45	69.6	(1)		41	71.9	33	57.8
Velvet Grass	112	51.4	64	57.1	59	52.6	93	83.0	77	60.7	69	61.6	50	44.6	78	78.9	41	36.6	(3)		60	53.1
<i>Notololcus lanatus</i>	85	39.4	56	65.1	55	63.9	74	86.0	63	73.2	58	67.4	46	53.4	67	77.8	33	38.1	60	69.7	(3)	
<i>Poa pratensis</i>																						
June Grass																						
<i>Bromus secalinus</i>																						
Average			62.4		58.6		83.8		72.3		64.2		48.6		69.2		39.8		68.0		57.6	

Total cases studied 300.
From Grubb and Vaughan.

Fortunately, not all pollens require a top dose of 20,000 units to provide relief. In our experience 10,000 or even 4,000 units of grass extract are often adequate. This may be due to the lower atmospheric concentration, to the lower toxicity of the pollen, or both, or to some other as yet unrecognized factor.

Combined treatment.—

9. *A patient experiences pollinosis in both the grass and ragweed seasons. How may the two treatments be combined?*

A single extract mixture is made up containing equal parts of mixed ragweed (giant and short) and the appropriate grass pollen mixture. Treatment is carried out with this prior to the grass season to reach a top dose of 20,000 units comprising 10,000 of grass mixture and 10,000 of ragweed. My experience has been not only that 10,000 units protect in grass pollinosis but also that it is not as necessary to drop the dose during the season. It would seem that the more toxic the pollen or the higher its atmospheric concentration, the more important it is to drop to a lower maintenance dose during the season. During the grass season, therefore, treatment is given every two weeks, the dose either being kept steady at 10,000 grass plus 10,000 ragweed units or dropped to about 4,000. The latter is preferable. In either case, after the grass season and a few weeks prior to the ragweed season, plain ragweed extract is added in increasing dosage. Four thousand units are withdrawn from the concentrated bottle containing the mixed ragweed and grass extract and to this there is added in the same syringe an additional 2,000 units of plain mixed ragweed extract. The next time 4,000 units are added. This is continued until, just prior to the ragweed season, the patient is receiving his 4,000 units of grass mixture

TABLE XLVII.—SCHEDULE OF COMBINED GRASS AND WEED TREATMENT

BOTTLE CONTAINS					
DOSE IN UNITS		WEED AND GRASS MIXTURE, EQUAL PARTS		WEED MIXTURE ONLY	EPGCH
GRASS	WEED				
To be given weekly or semiweekly	10	10	1:5,000—0.1 cc.		Prior to grass season
	20	20	—0.2 cc.		
	40	40	—0.4 cc.		
	70	70	—0.7 cc.		
	100	100	1:500—0.1 cc.		
	200	200	—0.2 cc.		
	400	400	—0.4 cc.		
	700	700	—0.7 cc.		
	1,000	1,000	1:50—0.1 cc.		
	2,000	2,000	—0.2 cc.		
4,000	4,000	—0.4 cc.		Top dose before grass season	
6,000	6,000	—0.6 cc.			
8,000	8,000	—0.8 cc.			
10,000	10,000	—1.0 cc.			
Biweekly	4,000	4,000	—0.4 cc.		Maintenance during season
	4,000	4,000	—0.4 cc.		
	To be held constant through the grass season				
Weekly or semiweekly	4,000	6,000	1:50—0.4 cc.	1:50—0.1 cc.	Prior to weed season
	4,000	8,000	—0.4 cc.	—0.2 cc.	
	4,000	12,000	—0.4 cc.	—0.4 cc.	
	4,000	16,000	—0.4 cc.	—0.6 cc.	Top dose before weed season
	4,000	20,000	—0.4 cc.	—0.8 cc.	
Biweekly	4,000	4,000	—0.4 cc.		Maintenance in weed season
	4,000	4,000	—0.4 cc.		
	To be held constant through weed season.				
If this is to be followed by perennial therapy, the dose will remain unchanged.					

and 20,000 units of ragweed. At the onset of the season if perennial treatment is to be continued, the schedule reverts to 8,000 units of the mixture (4,000 plus 4,000) biweekly.

In a case of this sort the total volume of material administered can be reduced by the use of 10 per cent extract. While there has been some division of opinion as to how concentrated a pollen extract may be made, recent evidence would indicate that an extract made up one in ten, weight by volume, does actually contain a proportional amount of the active substance.

The same program holds for other pollens.

Weeds and grasses.—

10. *A patient regularly experiences late summer pollinosis each year. Some years he also had trouble during the tree or grass season, but this is not a constant affair. Often he passes through the earlier seasons without symptoms. First consultation is around the middle of June. He gives positive skin reactions to the weed pollens and to some of the grasses or trees as the case may be.*

Preseasonal weed pollen treatment is given. If relief is adequate, perennial treatment is not instigated; if relief is not satisfactory he will be continued with perennial therapy. No preseasonal treatment will be given prior to the tree or grass season. If symptoms do develop at that time coseasonal treatment will be given, entirely independently of the perennial weed treatment which will be continued.

Tree pollens.—

11. *Patient has symptoms during the tree pollen season. He reacts to several tree pollens. The time of onset of symptoms varies from year to year so that it is difficult to determine which of the positively reacting trees are responsible for symptoms.*

During the first year at least, coseasonal therapy is the method of choice, the appropriate pollens to be determined by the trees which are found in flower when symptoms appear. If the patient lives nearby, the various species of trees may be examined during field surveys. If he lives at a distance, he may expose pollen slides thinly smeared with vaseline or cedar oil and mail them in for pollen identification.

Other Methods of Specific Hyposensitization

Rush inoculation.—This was suggested by Freeman of London in 1930. A few days prior to the onset of the season the patient is hospitalized and given injections of pollen extract every one and a half to two hours. Treatment is completed within from two to five days. Initial doses range from 20 to 200 units with an increase of 10 to 20 per cent on the preceding dose each time. This method is often accompanied by severe local reactions, and frequent constitutional reactions. Throughout the period the patient must be under the constant supervision of a trained nurse and physician. Adrenalin must be given for the constitutional reactions.

No method is acceptable which causes more discomfort or illness than does the disease itself or which might theoretically jeopardize the patient's life. A method in which constitutional reaction is the rule rather than the exception is to be avoided.

Topical desensitization. Mackenzie (1922) reported slightly better results in prophylactic treatment by combining with parenteral administration,

local instillation of pollen extract on the nasal mucosa in increasing concentration. The writer used this method in 1923. Patients were given graded concentrations, 1:5,000, 1:500, and 1:50. These were placed in an atomizer and sprayed into the nose twice daily, gradually working up to the concentrated extract. Preseasonal injections were also given. Results appeared similar to those following the injections alone.

Caulfeild (1922) applied a pollen ointment to the nasal mucosa with similar results. He felt that the combined use of the ointment with injection therapy was "slightly more successful than the simple injection treatment." Neither of these procedures is in general use at the present time.

Recently Francis (1938) has proposed the intranasal application of pollen extract coseasonally. Ten Noon units are applied. If this does not produce mild sneezing within 5 minutes, the dose is repeated. Subsequent doses may be increased by 25 per cent at intervals depending upon the length of time during which the patient remains symptom free. Concentrations are so adjusted that no more than 0.5 cc. need be given in a dose. In the event of pronounced local reaction the previous dose is repeated. The immediate effect is a short bout of sneezing with the usual symptoms of hay fever. The effects of this artificially produced attack are said to quickly subside, after which the patient becomes more resistant to atmospheric pollen. The writer has had no experience with this procedure. One might question its logic. Francis gives no statistical enumeration of his results.

Intensive two-week preseasonal course.—This was recommended in 1925 by Kahn and Grothaus, Duke, Bernton, Brown and in 1926 by Clock and Scheppegrell. The first preseasonal injections are given twice daily. Higher concentrations are given daily. According to Scheppegrell constitutional reactions were not frequent in spite of the fact that the dose was practically doubled each time, there being but five reactions in a series of 536 patients.

The writer tried this method in the 1929 and 1930 seasons. While constitutional reactions were not observed, delayed subcutaneous reactions were very frequent. The sore arms caused much complaint by the patients and necessitated delay in subsequent injections. As a consequence it was often impossible to reach the desired top dose.

Since these difficulties can be easily avoided by starting treatment earlier, the latter procedure seems far preferable. Since it has been shown that pollen allergen may persist in the blood up to 48 hours after injection and there is, therefore, the possibility of cumulative effect, the procedure would appear to be not without some danger. I know of one anaphylactic death in a patient receiving injections every other day which appeared to be due to cumulative effect. Injections not oftener than every third day or twice weekly are much safer.

Peroral desensitization.—Preseasonal desensitization by feeding pollen extract has been reported by Touart (1922), Black (1927), Thommen (1931) and Gatterdam (1933). Black and Thommen demonstrated that the antigen enters the blood and is excreted in the urine. Black demonstrated the antigen in the feces, indicating that not all is absorbed. Black, himself allergic to ragweed, took 5 per cent ragweed solution by mouth commencing with 0.1 cc. and increasing steadily with 3 doses daily to 2.5 cc. t.i.d. at the end of a week. The nasal mucosa was made less reactive. Nasal symptoms had followed the local instillation of 1:10,000 solution prior to treatment. Only a concentration of

1:1,250 or higher produced local symptoms after the week of ingestion. He reported gratifying therapeutic results in the 150 cases.

Thommen reported 90 to 95 per cent relief in one asthmatic treated orally before the season. In some cases he observed definite results, no apparent benefit in others. He remarked that the chief drawbacks were the large quantity of extract required and the variability of enteral absorption.

In 1934 the writer attempted coseasonal peroral therapy, using the same doses of extract that are given parenterally. Results were inconclusive. About one-third of the ten patients felt that they had derived some benefit although not as much as following hypodermic hyposensitization. In 1937 seven cases were treated coseasonally with extract prepared in capsule form by Eli Lilly & Company. One, with grass pollen conjunctivitis, appeared to be adequately relieved with capsules of the lowest concentration prepared, taken twice daily. Of the six who received oral ragweed therapy, four obtained no benefit and were changed to subcutaneous treatment; one failed to continue treatment; and one was completely relieved after taking capsules t.i.d. to a total of seven. Unfortunately for the study, this last is a patient who is consistently relieved each year for the duration of the season usually by one, rarely more than three or four coseasonal injections. Furthermore, conclusions were complicated by the low 1937 pollen prevalences. This was one of the two mildest seasons experienced in ten years.

Gatterdam (1933) has reported successful coseasonal treatment of cases of Bermuda grass and ash pollinosis, using 3 per cent extract. This concentration is first given, 3 drops in water thrice daily before meals. It was gradually increased to 15 to 20 drops. Later in the season 5 to 10 drops every second day sufficed for relief. Seven of 9 ash allergies experienced 90 to 95 per cent relief. One experienced about 60 per cent relief and 1 was not improved. Of 13 Bermuda grass cases, about one-half were adequately relieved coseasonally. In a later report (1934) 75 to 80 per cent of 81 cases were markedly relieved. Barksdale (1936) reported 88 per cent of 83 hay fever and asthma cases completely or markedly relieved following oral pollen or house dust hyposensitization. From the description of his method of extraction it would appear that the solutions were very dilute.

Stier and Hollister (1937) reported 78 per cent satisfactory results from coseasonal oral pollen therapy. Doses ranged from a few drops of 1:10,000 to 21 drops of 1:100 dilution. They dealt with the pollens of Washington and Oregon. These did not include ragweed.

Bernstein and Feinberg (1938) using ragweed extract observed practically no beneficial results even when sufficient material was given to produce marked gastrointestinal symptoms. They found the amount of the circulating antigen absorbed from the intestinal tract to be about 1/5000 of that circulating after subcutaneous injection.

It would seem that there is need for further study of peroral hyposensitization, both preseasonal and coseasonal. Black, who has always used extracts of pollen in his work with oral therapy, believes that the failure of many workers to get satisfactory results may be due to the fact that they used dry pollen. He believes that the amount of antigen absorbed from the intestinal tract is probably very small, and when dry pollen is used may be little or none. He believes also that those most likely to get satisfactory relief by oral treatment are those who get best results from hypodermic treatment with small doses. In his experience

the results with oral therapy are much better in children than in adults, and he thinks this may be due to the difference in absorption in the young and old persons. That ragweed antigen may be absorbed from the intestinal tract would seem to be proved by the work of Black and Shelmire, who found that after the ingestion of large amounts of ragweed extract the urine was found to contain the antigen in sufficient amounts to produce skin reaction in susceptible persons.

Intravenous desensitization.—Lichtenstein has attempted intravenous pollen desensitization and proved its possibility. Although he observed reactions and much of his paper is taken up with the discussion of them, he did find that preseasonal intravenous pollen therapy was highly effective. The technic is time-consuming, since it requires dilution of the required amount of extract in 20 cc. of saline and very slow injection. It seems doubtful that this method is likely to become popular at any time, but it is of interest in demonstrating the possibility of this procedure and in opening possible new methods of research.

Use of epinephrin with desensitizing injections. Some observers, notably Duke, recommend the giving of adrenalin with the pollen extract during preseasonal or coseasonal treatment, to prevent the contingency of systemic or constitutional reaction.

The writer has found no clear-cut contraindication to this practice. Where there is no tendency toward reaction, its use is unnecessary. In coseasonal therapy, adrenalin may be given in the same syringe with the allergen if the patient is having symptoms at the time, for the purpose of giving quick relief. It should be remembered that epinephrine may prevent the appearance of a local reaction while permitting sufficient absorption to overdose the patient.

Theoretically adrenalin given in the same syringe slows absorption of the allergen. Feinberg and Bernstein have shown that it does cause a delay in absorption, but that, once absorption has commenced, the antigen titer curve in the blood proceeds at an approximately normal rate. This may be interpreted as indicating that release of allergen from the point of deposit in the tissues is delayed but not that smaller amounts are released over a longer period.

Results of Specific Pollen Therapy

Alexander's survey of the treatment of hay fever by specialists in the United States and Canada previously referred to indicates that in a three-year period 91 allergists estimated their results as follows. From 90 to 100 per cent relief was obtained in 27 per cent of those treated preseasonally, 38 per cent coseasonally, 35 per cent of those treated both preseasonally and coseasonally and 49 per cent treated perennially. From 70 to 100 per cent relief was obtained in 82 per cent of preseasonal cases, 67 per cent of coseasonal, 91 per cent treated both preseasonally and coseasonally and 89 per cent perennially.

In my own series I find that, in round numbers, 80 per cent received adequate relief with coseasonal therapy, 85 per cent with preseasonal and 90 per cent following perennial treatment. By adequate relief is meant 75 per cent or better.

However, as Alexander and several other investigators have pointed out, a reliable percentage designation of this sort is quite an impossibility. Different observers select varying standards of adequacy. If the patient is left to judge it will be found that some complain very little of what appear to

be outspoken symptoms, while others bitterly resent the persistence of symptoms that are mild indeed. No evaluation of results is of any significance unless daily pollen counts have been made during each season. When little pollen is in the air, results with a given procedure will naturally be better than when there is much pollen. The type of pollen plays a great part, some varieties being more highly toxic than others. The adequacy of control of nonpollen allergens is of some importance. These and other less important factors make difficult any comparison of the results of different investigators or even of the same investigator from year to year.

In the present discussion, therefore, little is to be gained from an analysis of the reports of numerous investigators, and we shall content ourselves with generalizations which are a fair cross-section of their conclusions.

Prognosis to the patient.—Since the patient's first question is often, "What relief may I expect?" a reasonably accurate answer must be available. Even in the best of hands there are some cases of therapeutic failure each year. Rarely are they total failures, but the relief given is not adequate. From 80 to 90 per cent are usually adequately relieved under proper treatment.

A few cases of pollinosis are completely relieved, while more have some symptoms during the season especially on days when the pollen concentration is unusually high. On those days symptoms may be as severe as in the untreated case. Pollen cases usually have symptoms for six or seven weeks. Under proper treatment they may have symptoms for a total of as many days. Relief is usually more complete with trees and grasses than with weeds, especially the ragweed and artemisia or wormwood families. Also the top dose need not be as high. Paper mulberry, a tree with very toxic pollen, is an exception. The response in pollen asthma is usually as good as that in pollen hay fever. About 35 per cent of hay fever sufferers also have seasonal asthma.

Permanent cure.—It is safer to speak of relief than of cure in pollinosis. About 7 per cent are apparently cured following one or several years of treatment. Some of these again experience symptoms after a variable number of years. Of those who appear cured and require no further treatment, about 50 per cent continue to show positive skin reactions in spite of the absence of symptoms. These are due to the presence of reagin in the blood as demonstrated by passive transfer. The positive skin reaction may, therefore, be looked upon as an historical landmark, indicating past trouble as well as present difficulties.

Undoubtedly, some recover from seasonal pollinosis without any treatment whatever. I have found such persons when tested incidentally to other allergic studies, to give positive reactions to the appropriate pollens years after recovery. No information is available concerning the percentage of spontaneous cure. We do not know whether it corresponds to the percentage of apparent cure following therapy.

The fact that apparent cure following therapy does not appear to depend upon the total number of years of treatment nor upon the particular type of pollen therapy, suggests that we may actually be dealing with cases of spontaneous cure and that the treatment exerts little influence in this regard. Permanent relief may even follow a season of unsuccessful treatment.

Frequency of constitutional reactions. This varies with different observers and with different procedures. Eighty-seven allergists replied to Alexander's questionnaire on this point; 52 reported less than 1 per cent, 61

reported 1 per cent or less; 16 reported from 1 to 5 per cent, 10 from 6 to 10 per cent, 3 from 11 to 20 per cent and 1 reported as high as 68 per cent. These are probably systemic reactions rather than constitutional, in accordance with the writer's differentiation of these terms. The report does not indicate clearly whether the percentage is of patients or of injections. The higher incidences must include even the mildest type of reactions such as those listed by Peshkin and previously discussed under "perennial therapy." In our own clinic we average about 1 systemic reaction for every 300 pollen injections. They are usually mild. I have seen no cases of anaphylactic shock.

Disappearance of positive skin reaction.—In the early days of pollen therapy the effort was made to desensitize preseasonally to a point where the previously positive skin test reacted negatively. It was felt that such a person was actually desensitized. The disappearance of the positive reaction indicated adequate protection and could, therefore, be used as a prognostic control test prior to onset of the season.

There has been considerable discussion concerning the disappearance of the positive skin reaction following treatment. The majority appear to feel this cannot be taken as a guide to the thoroughness of protection. Spain and Markow conclude from a review of cases treated preseasonally over a number of years that after three or four years there is a lessened degree of cutaneous reactivity. However, this is of no value as a prognostic guide. That this latter fact should obviously be true is realized when we recall that not only individual reactivity but also the pollen concentration in the air and other factors, play a part in the intensity of the symptoms from year to year.

Lamson, Piness and Miller (1928) observed a decrease in skin reactivity to spring and fall pollens after desensitization. Colmes (1932) concluded that the completeness of protection may be measured by the diminution of the scratch reaction to the pollen. In a series of 44 cases the scratch reaction became negative following treatment in 9 per cent and was decidedly diminished in 81 per cent. In the remainder it was unchanged.

Colmes and Rackemann later found that good results were accompanied by diminution of skin reaction in the majority of patients. However, in 18 per cent good results were observed without any change in the skin reaction and in 11 per cent poor results were obtained even though the skin reactions did diminish. Furthermore, they found strong evidence that this was not a specific factor, since with individuals allergic to several pollens, treatment with one pollen diminished the skin reactivity to the other pollens at the same time. This same observation has been made by others, notably Lamson, Piness and Miller, Van Leeuwen and Gough.

Colmes and Rackemann remark that it would be interesting to observe whether treatment with one pollen extract would protect against symptoms due to other pollens to which the individual is allergic. Take, for example, a person allergic to grasses and ragweed. Desensitize him to the grasses, and see whether this alone would control his ragweed hay fever also. They state, "The temptation to treat the 'double cases' with ragweed is so strong that the question has not been answered by direct experiment. Perhaps in the near future someone will treat a group of patients with those pollens which give positive skin reactions but whose dates of appearance do not correspond with the dates of symptoms. The results will be interesting."

As a matter of fact we have done this repeatedly. We have had patients with spring and fall hay fever whom we have treated with ragweed extract only. A number of these have come in after the spring season, in time for pre-seasonal ragweed treatment. We have given the latter and then continued with perennial ragweed injections. If during the next grass season they have experienced symptoms in spite of perennial ragweed injections, we have given them coseasonal grass therapy for that period. And a large proportion have required coseasonal grass therapy. This would indicate that treatment with one pollen extract will not protect against another unrelated pollen even though the skin reactivity to the second pollen has been diminished. It is most difficult to draw quantitative conclusions. Although many require coseasonal grass treatment, none can say that without the ragweed injections they would not have required more intensive grass treatment. And a fair proportion do pass through the grass season without requiring treatment. This has been our observation often enough to justify our recommending perennial ragweed treatment with no grass treatment in the "double" cases, the latter to be held in abeyance until symptoms appear. If they do appear, coseasonal treatment is given.

The reverse practically never holds. In my experience, perennial grass treatment will not adequately protect against the much more toxic ragweed.

CHAPTER LIV

POLLEN AVOIDANCE. HAY FEVER RESORTS

The problem of weed control. The ragweed, with so many other weeds, is a product of soil cultivation and grows most profusely in ground that has been well prepared for it by previous preparation for a crop plant. The farmer carefully protects his fields from weeds during the growth of his crop but as soon as the harvest has been completed he loses all interest, allowing the weeds to run wild.

It is, therefore, but natural to find that the heaviest ragweed production and therefore the heaviest pollen production occurs in that section of the United States where farming is done on a large scale, in the basin of the Mississippi River and its tributaries.

Conversely, it becomes obvious that heavily forested areas or uncultivated mountainous sections are poor territories for the growth of ragweed. The lone hay fever sufferer on a camping trip in the woods of northern Michigan or in the Adirondacks or White Mountains found to his great pleasure that his hay fever unaccountably disappeared in one or another of these sections. He told his fellow sufferers and in the following years several visited the areas, confirming his observation. Soon such areas acquired a reputation as havens for pollinosis victims; boarding houses were built, to be followed later by magnificent hotels. To provide for the culinary needs of the growing communities, trees were felled and fields were planted. And ragweed seeds were brought in, probably mixed with crop seeds, fodder, etc. In this way many of the old famed hay fever resorts eventually lost their mysterious power to relieve, destroyed by the hand of man, the result of his humanitarian enthusiasm in telling his fellow sufferers of the glory of his newly discovered haven and his selfish insistence upon comfort along with relief.

The presence or absence of wide-flung forests and the spread of cultivated fields are not the only factors which control the growth of ragweed. Soil, rainfall and other climatic conditions play a part. In the eastern half of Texas where rainfall is adequate ragweed is sufficiently abundant to be a hay fever problem. In the western arid section there is no ragweed pollinosis. Durham tells me that he was unable to find ragweed in Cuba, that it is probably not a factor in the tropics, where virtually all plants are insect-pollinated, but that in all probability it will be found to again assume importance in the wheat fields of the Argentine.

Geographic variation. The spread of ragweed is virtually from the Atlantic Seaboard as far west as Denver, extending moderately up into Canada, and through this vast region of the United States virtually wherever man has seen fit to cultivate the soil. Beyond the western fringe of the ragweed belt, and overlapping it somewhat, we enter an area in which other weeds such as Russian thistle and the sages predominate as hay fever causes. Beyond the Sierras the grasses constitute the most important cause of pollinosis, although here as elsewhere many different kinds of pollens are responsible for a certain percentage of cases.

The problem of hay fever prevention must therefore be different in different sections of the country. In the East we need not even mention mountain cedar and mesquite which constitute such pressing problems in Texas. In Little Rock the trees are most important. When the oaks, hickories and pecans are pollinating, the yield is so profuse that nearby porches become covered with a layer of yellow pollen dust. This obviously cannot be prevented by any means short of tree destruction. In Texas the amaranths and the mesquites shed pollen which carries but short distances, and there might therefore be a possibility of some measure of control. In the neighborhood of Denver the problem becomes much more difficult, since in August eight different plants cause hay fever and many patients are allergic to a number of the eight. Allergic treatment must therefore be directed against several or all, to obtain adequate relief. There, Russian thistle is responsible for 80 per cent of the hay fever. There are six different kinds of sage, all of which cause pollinosis. Since these virtually cover the mountain side, their eradication cannot be encompassed. In Oregon, beyond the Cascade Mountain range, trees are especially frequent causes of hay fever. These include birch, alder, maple and oak but more especially willow and hazel. Grasses are especially potent factors. Velvet grass, a relatively infrequent offender in the East, is most important in Washington and Oregon. The coastal region of Washington and Oregon is the worst section of the country as regards English plantain which, however, is also distributed throughout the eastern section and causes many cases of hay fever. Plantain is especially hard to eradicate. One finds difficulty in removing it even from one's own lawn. Even the lawn mover will not cut the tough stems. We must realize, then, that the problem of prevention varies geographically.

Useful and useless plants. We may roughly divide those plants which cause hay fever into two classes, those which are useful and those which are useless. The trees and the grasses constitute the bulk of the former. Those so unfortunate as to be sensitized to useful plant pollens, fortunately the minority of the hay fever population, must grin and bear it or receive hypsensitization. I would venture to say that fully 95 per cent of pollinosis caused by useless plants in the eastern section of this country is due to ragweed. The remainder of this discussion will be limited to ragweed as an example of a "useless plant." There is plenty of ragweed pollen to cause symptoms. Durham has estimated that the annual deposit from the air in the United States amounts to at least one million tons.

Can hay fever be prevented in certain sections by means of weed control? Will weed campaigns in large cities and adjacent territories prevent hay fever? The answer, for the present, is most emphatically, no! This has been attempted often enough to have demonstrated its ineffectiveness.

Attempts at weed control. Chicago conducted a three-year campaign against ragweed. The first year, 1932, was merely educational. The following year there was an organized effort to eliminate the ragweed. During the third year \$165,000 was spent, with 25,000 men at work under city supervision, eradicating weeds. One is accustomed to think of a great metropolis such as Chicago as being very generally built up and rarely realizes how much waste land still exists in such communities. Vacant lots, and railroad yards constitute a high proportion of the total area and it is here that the weeds grow *ad libitum*. Nearly one-third of the total area within the city limits of Chicago is

wasteland; 25,000 workers were therefore none too large an army. The work may or may not have been well done, but when we realize that in spite of weed cutting, ragweed pollen was being blown into the city of Chicago from the farm lands through a radius of 50 to 60 miles, we can readily understand the ineffectiveness of the effort. During the season in which \$165,000 had been spent, the pollen counts in Chicago were higher than they had been in several preceding years. Hay fever was correspondingly severe.

A similar effort was made in Denver. During one season the city cut all weeds and the leading allergist had just as many patients as he had had in preceding years.

Duluth has long been considered a hay fever haven. When a visiting botanist reported reasonably large quantities of ragweed, the local hay fever club took exception. He was invited to address the club. He tells me that it was amusing to observe the group who in their loyalty to Duluth and its reputation had expostulated at his statement but who, during his talk, had their handkerchiefs to their noses a great part of the time.

Duluth then undertook a campaign of ragweed destruction which, unfortunately, died aborning. Five hundred dollars was set aside as a bounty on the weed. Children were informed that if they would pick the weeds and do them up into bundles of fifty, they would receive one penny for each bundle. I am told that within two days 6,000,000 plants were brought in. Since this was far more than the fund provided for, the campaign sponsors found it necessary to cry Halt!

We may conclude that for the present there is no possibility of pollen crop control in large cities, adequate to prevent or even diminish hay fever, unless the farmers throughout the countryside are as assiduous at weeding their fields after the harvest of their crop as they usually are before this time; and unless, at the same time, similar measures are enforced along the highways, railroad tracks and in river bottoms.

A hay fever Utopia.* Could we take an area, for example, an area in the mountains of New York State, in which ragweed has been found to be relatively sparse, and in which opportunities for its growth may be rendered even less propitious, and make of this area a hay fever asylum to which ragweed sufferers may journey, with assurance of relief?

Ragweed is a roadside weed. While it does grow in meadows and other waste spaces it grows more abundantly along the roadside, along the river banks, and especially where man has made its implantation easy in the cultivated fields. It does seem possible that with three cuttings the ragweed crop might be so materially lessened as to be beneficial to hay fever sufferers. There should be a first cutting, especially along the roadsides prior to the fifteenth of August, just before the ragweed pollinates. Weeds along fences and hedgerows would require attention. This would be followed by a regrowth which would require a second cutting toward the end of August. Finally, around the tenth to the fifteenth of September, there must be a third cutting not only along the roadsides, but also throughout the crop fields that have been previously cut over. It is decidedly questionable whether this would be economically feasible. It is true that ragweed seed does not carry far but the pollen is carried on the wind scarcely diminished for thirty miles

*Part of a discussion on the possibility of prevention of hay fever through public health measures at the Annual Conference of Health Officers and Public Health Nurses, Saratoga Springs, June, 1936.

and in diminishing concentration for another thirty and more. The total area that would require intensive weed control would therefore be great indeed.

It seems to me that the more practicable procedure to consider would be the reestablishment of conditions similar to those which existed in the early days of the hay fever resorts. This would involve the setting aside of a rather vast area in a section in which it is known that the conditions are not propitious to the abundant growth of ragweed. In this area which should have a radius of at least fifty miles practically no crop cultivation should be permitted and the roadside and railroad rights of way, if any, should be very carefully and adequately policed against ragweed.

The growth of plants inimical to ragweed growth should be fostered. Reforestation would be an important feature of this procedure. It is quite true that one would in this way be introducing other plants which cause hay fever in some cases, but they are plants which pollinate prior to the onset of the ragweed season and would, therefore, be of no significance to the person who at the moment was suffering from ragweed pollinosis.

Near the center of this vast reserve, preferably in a forest, the hay fever sufferer would find haven in scattered sportsmen's camps, quite primitive in set-up; in cabins scattered here and there through the woods or on the mountain-side; or if he prefers, in splendid modern hostelries with every comfort and convenience, even including air conditioning. There would, however, be one absolute requirement for the provisioning of the entire community within the preserve, that all foods be trucked in from the outside and that no land be allocated to grazing or crop raising.

This might appear to some as a dazzlingly ambitious project, but those of us who have watched the national activities of the last few years will agree that we are living in the day of dazzlingly ambitious projects. We are also living in the day of national reforestation and in the day of the acquisition of vast preserves for national parks.

Let us assume that such an utopian paradise for the long-suffering victim of the pollen of *Ambrosia elatior* has at last become an actuality. What problems will now confront us?

There are over 2,000,000 hay fever sufferers in the United States. Will they all wish to enter asylum together and at once? How can we crowd them in? How shall we reach a decision as to who shall be among the chosen and who must continue to suffer at home? Possibly this will be worked out automatically by a scale of charges depending upon the character of the accommodations, but all sufficiently high to eliminate the many. Who shall make these charges, the state or the nation? Or, shall it be the little business fellow who has moved in after the governmental authority has spent hundreds of thousands or millions preparing this Elysian field, staked out his claim and is now ready to do business with his temporary tenants at a personal profit and no great original expenditure on his part? Or, shall it be the great corporation which has been sitting watchfully on the sidelines while the taxpayers' money has prepared Utopia, ready then to rush in, build its palace and reap a handsome profit for its shareholders?

Indeed, either of these two classes coming in to root in the soil previously prepared by man is sometimes much more bothersome to one's disposition than is the lowly ragweed itself. No, it would seem more equitable for the state

or national government which has prepared the preserve to continue with control, organizing and supervising abodes for hay fever victims in a manner comparable to that already in force for tourists in the Yellowstone and other national parks, reaping for itself what financial reward, great or little, it chooses.

Overcrowding would probably not be an acute problem. Many of the well-to-do would still prefer a trip to Bermuda or Europe or to the Pacific Coast. Most of the wage earners would still find it economically preferable to receive pollen therapy, stay at home and work. Indeed, it is conceivable that, with continued advances in pollen therapy, there might be some difficulty in attracting an adequate transient population to justify the enormous original expenditure.

And then there is the possibility that in the end it will be found that a radius of fifty miles is insufficient. Possibly it should have been seventy-five. If I recall my geometry correctly, the area that must be reclaimed varies as the square of the radius. The expense entailed in spreading beyond fifty miles would therefore be not inconsiderable. And while we are attempting to guess at the minimal requisite radius, let us recall the dust storms which, originating in the dust bowl of Colorado and Kansas, deposited themselves in part on the snowcapped mountains of New Hampshire.

The advantages of a hay fever asylum within easy reach of the population centers of the North Atlantic Coast, as in the Adirondacks or the White Mountains, are obvious. Equally obvious is the statement that if such an asylum is to be prepared it should be done in the locality or localities that are already free from ragweed. Is it better to try to reclaim territories for this purpose, under any circumstance an uncertain procedure; or to find a territory which is already free from the weed and which may be utilized for the purpose, with weed contamination prevented by the application of present knowledge? Would such a place when found be too far from the population centers? Would hay fever victims be willing to go to the woods of upper Canada, for example? Would the cost of reclaiming an area reasonably near to New York and the other large cities, with its hazard of possible failure, be considered worth while by the taxpayers when we consider that only a relatively small proportion of the population, even of the hay fever population, would be able to utilize it?

Would the venture be justifiable in view of the recent very satisfactory improvements in the methods of allergic therapy which may now be applied at home?

I make no effort to answer these questions. Indeed, some could not be answered until after the experiment had been made and put to the test. Some of the questions, however, should be considered in the outlining of the experimental program, if success is to be achieved.

In conclusion I would say that with present methods and facilities the prevention of hay fever due to the pollens of weeds and grasses is not practicable in the large population centers. It might be possible to establish a territory *in a favorable location*, where ragweed sufferers would find relief. It is a great question, however, whether the attempt would be justifiable in view of the necessary expense, the uncertainty of success, the fact that similar locations are already in existence, and that modern methods of treatment enable many of the sufferers to remain at home in comfort.

Hay fever resorts. Chambers of Commerce or other organizations in the following localities issue pamphlets claiming local freedom from hay fever. Obviously, one can safely say no more than that a proportion of ragweed sufferers appear to gain some relief while there.

The most recent survey, by Durham (page 524), is based on actual pollen counts at the localities studied. For each locality he determines the total number of pollen grains deposited upon unit areas of slides for the entire ragweed season; the maximum deposit for any single day; and the total number of days in the season on which the count was higher than 25 and therefore presumably high enough to cause symptoms. On the basis of these three figures he established an index for each locality. Cities with pollen index of zero had no days in which the count was more than 25 and the total deposit per unit area did not exceed 200.

CHAPTER LV

SPECIFIC TREATMENT OF ALLERGY TO INHALANTS OTHER THAN POLLEN

Inhalant allergens other than pollen are more likely to cause perennial symptoms. It is more logical, however, to speak of nonpollen allergy or non-seasonal allergy since the frequency of exposure chiefly determines whether symptoms shall be perennial or irregularly intermittent. A person allergic to horse dander will not have symptoms throughout the year if he is not constantly exposed to the excitant. On the other hand, one who is allergic to pyrethrum may have seasonal symptoms if he is exposed to insect powders and sprays only during the summer months. Again, pollen may very occasionally cause symptoms out of season. Wilmer* has observed a man allergic to ragweed pollen who experienced symptoms when in his library at any time of the year. Examination of dust from the tops of the books showed ragweed pollen, even in the winter. Pollen may be considered as a possible etiologic factor in dust accumulations of this sort.

We may say, however, that, in general, symptoms from inhalant allergens other than pollen are not definitely referable to any special season. Exacerbations occur at rather irregular intervals. Symptoms may be more or less constant if exposure is similarly constant.

There are certain potential allergens to which we are all exposed practically daily, and which may be responsible for perennial symptoms. The commonest are house dust, orris root, feathers, pyrethrum, tobacco, silk, kapok, animal emanations and, less often, fungi, including the yeast group.

Principles.—The general principles of specific therapy are similar to those employed in pollen treatment: (1) avoidance when possible; (2) desensitization; (3) hyposensitization with small doses on the basis of coseasonal therapy.

Avoidance.—When feasible, avoidance is the procedure of choice. There is evidence strongly suggesting that in some persons at least, there is a natural tendency toward loss of sensitization provided repeated exposure can be avoided.

Even if avoidance cannot be made complete, lessened exposure may be sufficient for relief and will improve results from specific treatment. The period of avoidance necessary for loss of sensitization varies with the individual, depending upon the degree of sensitization and the nature of the allergen. Some may successfully reestablish exposure after a few months, but here we are not dealing so much with loss of sensitization as with partial loss, with resulting increased tolerance. We may speak of such patients who, although still sensitized, can tolerate exposures of reasonable degree as being in a state of allergic equilibrium. The equilibrium may later be upset following an overdose of the excitant or following the action of nonspecific factors such as constipation, fatigue, emotional upsets, infection, etc.

In a series of migraine cases, the writer found that of those who found that after a period of avoidance they could again eat the offending foods, the

*Wilmer, Harry, Philadelphia. Personal communication.

average period was 4.5 years. Even then, the cure is not always complete. Thus, in this series "cures" such as the following were recorded: "Mrs. B. can eat all of the forbidden foods except fish and cabbage. With Mrs. F. the foods cause symptoms only when she is fatigued. Miss S., allergic to wheat, can sometimes eat it for as long as three to five weeks, but eventually develops headache therefrom. Mr. G. states that wheat or beans eaten at one meal will cause no symptoms, but will do so if eaten for six meals straight. Miss O. can eat all forbidden foods in moderation but not in excess." One-third of the series found that after avoiding prohibited foods for from four to ten years, they were still unable to eat them.

These findings are comparable to those which follow the avoidance of inhalants. Since it is usually impossible completely to avoid the allergenic inhalants for such long periods, it is often necessary to employ hyposensitization.

Desensitization.—Here, we meet an apparent paradox. If sensitization may be lost following avoidance, then this is the method of choice. If avoidance will result in cure, then repeated exposure theoretically will delay cure. If this is so, desensitization by repeated injection of the allergen is not proper treatment. On the other hand, if repeated exposure, as by injection, will increase the patient's tolerance to the offending allergen to that point at which exposure causes no symptoms, the procedure appears altogether rational.

There is as yet no answer to these two apparently contradictory arguments. Nor will one be forthcoming until we have learned why persons become allergic to this or that allergen in the first place, and why or how these sensitizations sometimes disappear spontaneously. For the present we must content ourselves with the recorded facts, that either avoidance or gradual acclimatization by repeated exposure of small degree relieves symptoms. Of necessity, the latter method must often be employed.

Desensitization to an allergen such as house dust is carried out along the same program as for preseasonal pollen desensitization. House dust extract, concentrated as much as possible in its extraction and containing an unknown quantity of the specific dust excitant, is termed "concentrated." Serial dilutions from this are termed 1:10—1:100, etc. Our experience has been that an initial desensitizing dose of 0.1 cc. of 1:10,000 concentration is safe. Not over one patient in 600 is so highly sensitized to dust as to experience systemic or even local symptoms from this dose. When rarely this does occur, the initial dose must be further reduced to 1:100,000 or even 1:1,000,000. Such an eventuality can usually be foretold by the intensity of the diagnostic skin reaction. The Endo dust concentrate is more active than the usual extract and should be used in smaller doses and increased with caution.

Successive doses may be increased in accordance with a schedule similar to that outlined for preseasonal pollen therapy. Injections are best given twice weekly. As a rule, they may be increased more rapidly, with a doubling each time. The final concentration may be of 1:10 or even concentrated dust extract. After this has been reached, the frequency of injections may be reduced successively to once weekly, once in two weeks, and once monthly. After several monthly injections have been given, treatment may be discontinued, to be resumed later, on return of symptoms. Since, in most cases, symptoms do return after a few months, the more customary procedure is to continue monthly injections for a long time, even several years. As in pollinosis, some who have had prolonged treatment find that they can discontinue it permanently.

Small dosage hyposensitization. This method was described by the writer in 1932. The logic of the procedure is similar to that of coseasonal pollen therapy, on the assumption that treatment is commenced during the season and that the season is 52 weeks long. We observed during the course of desensitization to perennial inhalant allergens that as a rule the patient was promptly relieved after two or three injections even though the concentration was 1:10,000. This being the case, adequate relief having been obtained with low dilution, it seemed unnecessary to proceed with further increases. Therefore, as soon as the patient was adequately relieved, no further increase was made. Usually, the dose remained somewhere in the concentration of 1:10,000 although at times it was necessary to increase to 1:1,000 before adequate relief was achieved. As soon as this occurred, the dose was fixed at the relief level. While injections were first given at semi-weekly intervals, this could often be increased following relief to once weekly, once every ten days or even once every two weeks. Longer intervals usually resulted in a return of symptoms.

If treatment must be continued for a rather indefinite time, it seemed as logical to stop at a concentration which gave relief as to increase to "concentrated" extract, especially when the latter was but a phrase with no true significance. There is no proof that results are more permanent with so-called concentrated extract. The only difference is that with the latter, intervals between injections may be lengthened to once monthly or longer.

If symptoms return after a period of low dosage treatment, there is a wide margin for further increase to a new level at which the symptoms may be relieved. This new level may be maintained, with margin for further increases if necessary.

We have been so impressed with the rapid amelioration of symptoms early in the course of desensitization with perennial inhalants that, when relief does not occur early, we rather anticipate that it will not occur even when we reach the highest concentration. This usually turns out to be the case. If relief is not obtained with 1:10,000 or 1:1,000 concentration or at least in the 1:100 concentration, one might as well discard the therapeutic extract and make up a different one with the hope of getting better results.

Relative advantages of low and high concentration dosage. In our own work we use both procedures. A patient who has remained under our direct supervision through the course of treatment and who can report frequently to the office receives low dosage therapy. If circumstances require him to discontinue treatment for a period of from one to three months, as may happen during vacations, journeys, etc., the concentration is increased prior to temporary discontinuation of treatment.

With persons sent in from a distance, in whom we cannot control the regularity of treatment, higher dosage therapy is employed, with gradual increases, usually up to 1:10 concentration. The one advantage of higher dosage is that the interval between injections may be longer. Since the patient may be careless in reporting to his physician, it is safer to employ higher concentrations under these circumstances.

There are certain circumstances in which high dosage must be employed. This is especially true in occupational allergy when exposure is unusually heavy. This applies to those whose duty or pleasure requires frequent close exposure to horses or other animals, to furs, etc. Here, higher doses may be requisite for adequate relief. But even here, as a rule, surprising relief occurs early in treatment when the dose is still small.

Duration of treatment. There is no established period of therapy in perennial inhalant allergy. After the patient has remained free of symptoms for several weeks or months one may increase the interval between injections until they are three or four weeks apart. If no symptoms have recurred during this period of lengthening the interval between doses then the amount of the injection is gradually decreased. If permanent relief has been secured the dose may gradually be reduced to zero and the patient remain well. Since skin tests frequently remain positive long after the clinical sensitivity is lost, they cannot be used as a criterion of cure.

Substitution of allergens.—Dust has been referred to in this discussion chiefly because it is the most frequent perennial inhalant allergen and one for which therapy is often necessary. Some allergens vary little no matter what the source. This is not true of dust. As a stock testing material one may make up a dust extract which is a composite of a large number of autogenous dusts all of which have produced unusually good reactions in sensitized persons. This is termed "stock dust." This is usually satisfactory for testing and treatment. Autogenous dusts are seldom required. All the work done in recent years indicates that there is a common antigen in most dusts which has been amply confirmed by the work of Boatner, Efron and Dorfman.

Inhalant allergens.—Although statistical analyses by different observers will vary depending upon the locality, occupation and social status of the individual, the relative importance of the common inhalant allergens as outlined by Cooke and Vander Veer (Fig. 10) will hold for the most part, anywhere in the United States. The outstanding exception is the pollens, which vary with location. The list is in no sense complete since there are occasional instances of inhalant sensitization to any number of unusual allergens. If we should include occupational dusts, a large list would be added, some of which would be rare in one locality, common in another.

Multiple inhalant sensitization. Persons are often allergic to two or more substances which cannot be avoided, such as house dust, feathers, orris root, and pyrethrum. These may be combined into one allergen mixture. Let us assume, for the sake of simplicity, that there are but two allergens to be mixed. Let us assume that they are each available in 1:10,000 and higher concentrations. Should they be mixed so that the final dilution is 1:10,000 of each? If they are mixed, 1:10,000, in equal parts, the final dilution will be 1:20,000. As a matter of fact, this is of no great importance. The 1:10,000 concentration is purely arbitrary and relief is often obtained with higher dilutions. Therefore, there is no objection to mixing together several extracts of 1:10,000 concentration. Obviously, if there are a large number, from 7 to 10, one may mix 1:1,000 dilutions, to more nearly reach an original concentration of 1:10,000 of each in the final mixture.

Combination with pollen extracts. If a patient who has had preseasonal treatment for pollinosis does not respond adequately during the season, he may (1) be placed upon a diet in which positively reacting foods are excluded, (2) be given coseasonal pollen treatment with reduced dosage and (3) receive coseasonal hyposensitization with other inhalant allergens to which he reacts, such as orris root, pyrethrum, etc. One may therefore have occasion to make up 1:5,000 pollen extract for coseasonal treatment. Other inhalants may be incorporated. The simplest procedure is to add the dust or other extracts in such a small volume that it will not materially alter the volume of the 1:5,000 pollen

extract. Thus, one may prepare treatment material containing 5 cc. of pollen extract, to which is added 0.05 cc. of 1:100 dust extract. For practical purposes, this represents then 1:5,000 pollen extract with 1:10,000 dust extract, since the 1:100 dust extract has been diluted another one hundred times. Other allergens may be added in the same way.

NOTES ON NONSEASONAL INHALANT ALLERGENS

House Dust

The actual excitant in house dust remains as yet unidentified. There is evidence that it is derived in part from deterioration of materials in upholstery, draperies, rugs, clothing, etc. At times a more potent extract may be made from dust collected from mattresses, upholstered furniture, etc., than from dust



Fig. 220.—Angioneurotic edema of the left side of the face and of the right hand due to inhalation of house dust. Location in these two areas was quite constant. Flare-ups occurred when there was dusting at home. Relief followed dust hypsensitization. This is an example of the fact that allergen inhalation may produce symptoms beyond the respiratory tract.

picked up from the floor by the vacuum cleaner. Some house dusts appear to be more highly allergenic for certain persons than do others.

Stock house dust extracts are usually made up as a mixture of a number of strongly positive autogenous extracts. Autogenous in this instance implies that the dust is obtained from the patient's own home, office, etc. Since some house dusts are more highly allergenic than others, once a good source has been found, it may be used repeatedly for stock extract. The writer found that the dust obtained in the vacuum cleaner from a certain local hotel gave strong reactions in most dust allergies. This provides a constant and abundant source. A colleague living in New York similarly uses dust from a certain apartment building.

Directions for obtaining autogenous dust.—The patient is directed to return home, remove the bag from the vacuum cleaner and substitute in its place a square of muslin about the size of a man's handkerchief which is tied over and around the outlet. The vacuum cleaner is then to be run over the mattress and pillow, top and bottom. Often as much as a teaspoonful of dust may be obtained in this way. This is to be labeled "mattress and pillow dust" and sent in for extraction. Similarly, specimens may be obtained from suspected articles of furniture, draperies, automobile upholstery, etc. In addition the patient is directed to send in a cupful of general house dust obtained from the bag of the vacuum cleaner for extraction as autogenous general house dust.

If desired, small light weight hand vacuum cleaners are available for making collections from mattresses and furniture. The allergist may keep one of these available for loan to patients who do not have vacuum cleaners.*

If no vacuum cleaner is available, dust from a carpet sweeper or that obtained with a broom and dustpan may be used. Naturally this is not as effective for furniture.

A patient who fails to react positively to stock house dust or fails to respond to treatment in spite of positive reaction may do better with autogenous dust, either general house dust or dust from the mattress or other special articles of upholstered furniture.

Dust avoidance.—Complete avoidance of house dust is usually impossible. In general, a dust allergic does better in a new house and in one with a minimal amount of upholstered furniture. A new house alone will not do the trick if one carries into it all of the old dust-producing furniture. I believe that much of the apparent increase in dust sensitization may be traced to the much more general use of overstuffed upholstered furniture. The search for comfort sometimes results in discomfort.

Directions for Avoiding and Removing House Dust

1. Renovate the house or room, but while this is being done, *you* keep away. We have seen dust allergies thoughtlessly go home to get the dust out of the house themselves!
2. Take down all draperies, curtains, hangings. Take up all rugs.
3. Either send them to be cleaned or have them cleaned outside the house. A vacuum cleaner, dry cleaning, and soap and water do wonderfully.
4. Remove all pictures and other dust catchers. Wash what may be washed and clean the remainder with a damp or oiled cloth. Store away until cleaning is finished.
5. Clean the picture molding with oiled cloth, and dust down the walls. Hot air heating is not satisfactory. Seal such flues, also other holes where dust might enter.

*One such is sold by the Singer Sewing Machine Company.

6. Go over all furniture with oiled cloth or damp cloth—top, bottom, front, back, inside, and outside. Pay especial attention to bed springs and slats, rear of chiffoniers and chifforobes, etc. Cover furniture with sheets until remainder of cleaning is completed.

In your bedroom use plain iron and wooden furniture that can be washed each week. Do not use cloth-covered box springs. All bedclothes must be washed each week. It may later be necessary to cover the mattress with a specially made envelope of rubber sheeting or fabricoid. This may be made by a mattress maker, or purchased from the Allergen-Proof Encasings Company, 4046 Superior Avenue, Cleveland, Ohio, or from Expert Bedding Co., 2454 No. Halsted St., Chicago.

7. Wash down woodwork, floors, radiators, etc.

8. After things are again set up, it is best to have no cloth rugs, in the bedrooms at least, and only such draperies as may be washed. Rag rugs and draperies are to be washed frequently.

9. Try to keep it that way!

10. Vacuum cleaning may be allowed, but not dry sweeping. If a broom must be used, sprinkle torn bits of paper soaked in water generously over the floor before starting.

11. Allow no animals in the house.

12. Look to see if there are damp, moldy, mildewy areas in the house (kitchen, bathroom, cellar, ceiling), and if so report to the doctor. He may then want to test you with molds.

13. If satisfactory avoidance is difficult, desensitization is usually satisfactory.

Type of vacuum cleaner.—Obviously, a dust allergic should not undertake dusting. If he or she must do so the vacuum cleaner is preferable to the broom. The writer has seen some persons who even experience hay fever or asthma when using the vacuum cleaner, due presumably to the small amount of dust which escapes through the bag. Cleaners containing filter pads or blowing the dust through water are much to be preferred by the dust-sensitive person.

Protection in dusty occupations.—Some dust allergies are so unfortunate as to be in dusty occupations which preclude avoidance and which result in such extensive exposure that desensitization is ineffective. Dust respirators may be used. The writer finds the Dupor Respirator No. 24 and the Willson Respirator adequate. The former, approved by the Bureau of Mines, provides rather easier ventilation.* The latter possesses the advantage that filter pads are easily renewed.

Illustrative cases.—A child highly allergic to house dust, living in a home heated by hot air, had severe asthma, presumably due to the dust circulating through the hot air flues. When the furnace was cut off and grate fires were lighted instead, her asthma was relieved.

Seward tells of a man living in Roanoke allergic to library dust. He sent to the State Library at Richmond for a very old book which no doubt had been on the shelf undisturbed for many years. As soon as he opened the package he had a severe attack of asthma and found it necessary to return the book without using it.†

Mattresses. Mattress dust sensitization is sometimes controlled by procuring a new mattress, even though it be of the same material. Usually a more effective solution is a mattress cover made of rubberized or other non-permeable cloth. Mattress covers with or without zippers made to size are commercially available. Mattresses made of pure silk ravelings may be used by those not sensitized to silk.‡ An all rubber mattress made on the principle of the rubber sponge is available and has been recommended by the superintendents of a number of large hospitals.

*Dupor Respirator made by portable Lamp and Equipment Co., 72 First Ave., Pittsburgh Pa. Willson Dustite Respirator No. 2, Willson Products, Inc., Reading, Pa.

†Seward, Blanton P., Roanoke, Va. Personal communication.

‡Allergia Products Company, 99 Chapel St., Newton, Mass.

Pullman asthma.—Some cases of asthma and hay fever become very much exaggerated from travel, whether it be by automobile or train. By car, one is necessarily exposed to higher concentrations of the pollen of the countryside. By train there is often the added possibility of allergy to some of the many allergens present, especially in Pullman cars. This includes feathers, orris root, probably pyrethrum, silk, horse hair, and the like. As it goes along, the train also stirs up tremendous amounts of dust, carrying with it the pollens of the roadside.



Fig. 221.—Two varieties of dust respirators, for use in dusty occupations. They may be used by pollen allergics, dust allergics, etc. Willson (left), Dupor (right).

Barrett has exposed pollen plates in various portions of a railroad train, in an automobile, and on an electric interurban car. He found the pollen deposit 2.7 times higher in a Pullman car than at his nearby pollen station at Salt Lake City. In an automobile in which vacuum action tends to hold the dust to the car, it was 4.7 times as heavy; in the electric train 6.2; on a locomotive cab 7.2, and on the observation platform of the train, exposed to the highest concentration of dust and vacuum, 8 times as heavy as at his Salt Lake City control station.

Air-conditioning of Pullman cars has very materially improved this situation, although some physical allergies do not tolerate the cool air and there are still those who experience difficulty when exposed to Pullman dust. The writer saw one woman living in New York who regularly developed severe asthma when on Pullmans and therefore traveled customarily either by bus or by airplane.

Nature of the house dust allergen.—Many dust ingredients have been suspected but the actual excitant has not as yet been positively identified. Cohen (1935) following the suggestion of Cazort, found that sterile cotton

linters which, when fresh, did not produce positive skin reactions in dust asthmatics, did do so after the linters had aged and deteriorated. Cazort later confirmed this (1936). These authors suggest that the house dust allergen is a deterioration product of cotton or that it may represent a deterioration product of various types of fibers. The original fibers need not be allergenic but at some stage in their ageing they may develop a substance which is chemically more or less common to all, and which represents the dust excitant. Boatner and Efron (1942) described the preparation of concentrates from house dust by subjecting aqueous extracts of house dust to two successive fractional precipitations with dioxane, two successive precipitations from concentrated ammonium sulfate solution, and dialysis. The purified fraction exhibits the properties of both carbohydrates and proteins. Its behavior with pepsin, heat, acid, and base indicate that it is a stable substance of protein nature. Material prepared in this way is quite potent and specific. It may be obtained commercially.*

Feathers

Feathers are, next to dust, the commonest excitant among nonpollen inhalant allergens. When one realizes that most persons spend approximately one-third of their lives, the eight hours of the night, with their noses quite well buried in feather pillows, one can understand the frequency of this sensitization. Evidence that it is an acquired allergy is found in Peshkin's early work in which he found that a large group of Jewish children sleeping on rabbit hair pillows were sensitized to the latter but not to feathers.

As has been brought out, one may be sensitized to feathers from any type of fowl (organ specificity) or one may be sensitized only to the feathers from chicken or duck or goose, etc. (species specificity). Since the former is more frequent, one who is sensitized to feathers is usually advised to avoid exposure to dust from any feathers.

A woman allergic to feathers continued to sneeze at breakfast time in spite of avoidance. She then realized that her negligee was trimmed with Coq feathers. Thereafter she breakfasted in another negligee and no longer experienced sneezing.

Directions for the Avoidance of Feathers

There are very few homes in which feathers are not widely distributed through most of the rooms. Feather pillows are in the bedroom, also often "down" comforts, and occasionally, feather beds. Overstuffed furniture in the bedroom or living room usually contains some feathers. Canary birds and occasionally parrots may be a prolific source of feather dust. Poultry in the back yard, pigeons next door, and rarely even birds' nests just outside the window may provide sources of trouble for the person who is allergic to feathers.

In extreme cases it may become necessary to remove all feathers from the house. As a rule, however, it is only necessary to render the bedroom completely free from feathers and feather dust. This provides about eight hours during which the patient is free from contact with feather dust and this is usually enough, especially if the patient is at the same time receiving desensitization with feather extract, to enable him to tolerate the small amount of exposure that he has elsewhere during the day.

All feathers must be removed from the bedroom. Pillows should not be stored in an adjoining closet since the dust from gradually disintegrating feathers slowly permeates the closet and seeps out into the room when the door is opened.

*Endo Products Inc., Richmond Hill 18, N. Y.

A kapok or silk floss pillow may be substituted for the feather pillow if you do not react to kapok, but unfortunately an allergic individual tends to become sensitized to kapok after prolonged exposure. Therefore it is better to cover the feather pillow with a dust proof slip.

Inexpensive dust proof pillow covers may be obtained from the Allergen-Proof Encasings Company, 4046 Superior Ave., Cleveland, Ohio, Expert Bedding Co., 2454 N. Halsted St., Chicago. The advantage of the cover with zipper lies in the fact that it may be carried along when traveling. (The cover without zipper must be sewed on permanently so that no feather dust can escape at any point.)

To completely seal the pillow cover, after the zipper has been closed, it is well to seal the zipper strip with a strip of waterproof adhesive one inch or one and one-half inches wide. An ordinary pillow slip may be put on over the dust proof cover.

Feather dust becomes generally distributed throughout any bedroom. This consists of small microscopic particles of the scale from feathers which can be easily seen if one will shake a feather pillow in a shaft of sunlight as it comes in through the window. It therefore becomes important to make the bedroom as free from dust as possible and thereafter to keep it that way. All dust catchers and dust makers should be removed from the bedroom.

There should be no draperies or the draperies should be washable and should be washed frequently. There should be no rugs other than rag rugs which can be washed at least once a month. There should be no upholstered furniture and all of the furniture should be gone over regularly once or twice weekly with an oiled cloth or washed. No dust should be allowed to accumulate behind pictures or behind or under furniture, in closets or elsewhere. The door should be kept closed so that dust from elsewhere in the house does not gradually seep in and contaminate the room.

Discussion.—Some years ago allergists customarily recommended kapok as a feather substitute in pillows. However, it soon became evident that a high proportion of patients rapidly became sensitized to kapok. This is therefore little used as a substitute at present. Silk ravelings used in special pillows (see mattresses) are a satisfactory substitute provided one is not sensitized to silk. The simplest and apparently most effective method is the covering of the feather pillow with a dust proof fabric. The writer finds those commercially available and equipped with zipper for removal, adequate in most cases. An advantage is that they may be carried when one is traveling. If one prefers to do without pillows one should bear in mind that they must not be on the bed in the daytime as well as not at night since feather dust sifts down onto the sheet. Some patients place pillows under the mattress, thus raising the head of the bed slightly. Horse hair or felt pillows may be used if one is not sensitized to their ingredients.

If one finds oneself in a hotel and has forgotten his pillow cover, a fairly satisfactory, although noisy, pillow cover may be made by telescoping two paper laundry bags over the pillow. These are covered with a fresh pillow cover. On a Pullman car the grey paper hat bags may be used. In the absence of any of these, the pillows may be discarded. One should, however, sleep with one's head toward the foot of the bed where no feather dust has sifted down.

Rubber pillows made of "sponge rubber" are available and pillows of glass fibers are being manufactured. These are quite comfortable and quite durable and are entirely free of any sensitizing substances.

Orris Root

The powdered root of the Florentine iris is widely used in the manufacture of cosmetics, perfumes, etc. The value of orris root powder lies in its flesh color, the fact that it clings smoothly to the skin, and that it serves as a mordant for

perfume, retaining the odor. It has a pleasant odor, resembling that of violets. It may be a constituent of face powders, talcum powders, tooth powders and pastes, shaving creams, sachets, cleansing creams, cold creams, bath salts, etc. It was formerly used in adhesive plaster. During the recent war the supply of orris was cut off and its use largely stopped. It is not found in face powders or talcums as formerly and is no longer used as a dry shampoo. Orris oil may be used in scented soaps, toilet waters, smelling salts and hair tonics. Tincture of orris may be a constituent of skin creams, cucumber cream, sunburn lotion and complexion beautifiers.



Fig. 222.—Orris root. The iris plant and large fleshy root from which orris root powder and oil are derived.

A chief difficulty in the avoidance of these types of preparations is that most of them are proprietary, made with secret or semisecret formulas, and that it is difficult to learn of the constituents. In the last few years, since recognition of orris root as a frequent allergen has become widespread and the war cut off supplies, manufacturers have ceased to use orris root in their preparations. Orris oil is used in moderate amounts at this time. Other ingredients may be the cause of trouble. Most reputable manufacturers are now willing to cooperate in determining allergenic substances in their products and some will provide their formulas on request. A few concerns have shown great interest in collaborating with the medical profession in the preparation of cosmetics and similar materials which are truly nonallergenic for the particular individual. These concerns will name all constituents and most of them will prepare special cosmetics for a given case if it has been found that that case is sensitized to any one or more of the usual ingredients of their products. The writer has felt that such concerns should receive the support of physicians since it is upon them that one must rely for individualized service to the patient.

Other cosmetic constituents.—It should be borne in mind that when a cosmetic is under suspicion the patient should be tested with the particular cosmetic which she is using, whether or not it is said to contain orris root. Other constituents might be causing trouble. Manufacturers of cosmetics made especially for the allergic individual and, as far as is possible, made of non-allergenic materials, have now made available the various powders, creams, oils, shampoos, lotions, and other cosmetic materials. No such material may be said to be "nonallergenic" since some persons may be found who are sensitive to any of the constituents even though these are chosen for their innocuous behavior. But, for most persons, they are entirely satisfactory. These include Almay, AR-EX, Frost, Mansfield, Marcelle. These are usually available at drug and department stores.

We have said much of the acquisition of sensitization following prolonged exposure. Black has described an interesting example. A woman, known reactive to orris root, worked in a beauty parlor where her duties consisted chiefly of giving orris root shampoos. This produced asthma and nasal blockage. She was found nonreactive to buckwheat flour. Since this could be used as a substitute she substituted it in her work for ten months, after which she developed asthma and was now found reactive to buckwheat. She was found not sensitized to rye flour. This was substituted in her work. The change was followed by relief for about a year after which, with return of asthma, she was now found reactive to orris root, buckwheat, and rye. Barley and rice flours were negative. She changed to barley flour with consequent relief to the time of writing (8 months).

In this case both clinical experience and the negative skin reactions indicated that the patient was nonallergic to all except orris root until after prolonged exposure.

Lambright and Albaugh reported a case of rhinitis with itching and burning of the eyes and nose, lachrimation, rhinorrhea, obstructed nasal breathing and malaise, shown by intracutaneous test to be due to the lycopodium used in a scalp powder recommended for oily scalps. The patient was relieved on avoidance and again experienced symptoms following re-exposure. Two friends with similar symptoms were relieved when she advised that they also avoid the powder.

Bullen has described perennial hay fever from Indian gum (Karaya gum) used in wave set material. Indian gum is also used in some foods such as custards and ice creams to make them hold their shape when cut. Asthma from flaxseed in wave set material, first reported by Grant, is quite common.

Pyrethrum

This common constituent of insect powders and sprays is the dried powdered flower of the pyrethrum plant, a member of the chrysanthemum family. It is grown principally in Asia, southern France and California.

A surprising proportion of the inhalant allergic population will state even prior to testing that symptoms increase when they are exposed to insect powders or sprays either in the house or in the garden. Pyrethrum allergy may be seasonal, due chiefly to the fact that the materials are used seasonally. Pyrethrum exposure may also follow the use of moth preventives in closets.

Some friends of the writer have six dogs. During the summer the dogs are repeatedly sprayed with Flit. Two of them promptly develop vasomotor rhinitis which lasts several hours each time they are sprayed. The others do not.

Avoidance at home is usually easy but may be difficult away from home, in the houses of others, in theaters and other public places. The process of moth-proofing carpets, upholstery, draperies, in homes and especially in dark moving picture theaters where moths are likely to congregate, usually consists in impregnation with a compound containing pyrethrum or one of the other insecticides to be mentioned below. Piness has reported fatal anaphylactic shock in a person allergic to pyrethrum who intentionally went into a theater to test out his reaction.

As a consequence desensitization is often required in addition to as much avoidance as can be carried out. Desensitization with extract of pyrethrum as with dust, feathers and orris root and most other inhalant allergens is usually satisfactory.



Fig. 223.—Pyrethrum.

Other insecticides. Lethane. Lethane is a trade name for an aliphatic thiocyanate widely used in insect sprays either alone or with pyrethrum.* In prescribing a spray containing lethane as a substitute one must make certain not only that the substitute contains lethane but also that it does not contain pyrethrum.

*Manufactured by Rohm and Haas Company, 222 W. Washington Square, Philadelphia, Pa.

"Lethane 384" is used only in sprays, not as a powder. Sensitization to this synthetic has not yet been reported but past experience indicates that it will probably occur at some time. Testing for sensitization to a spray containing lethane should be done by the nasal contact method, inhalation of air into which the material has been sprayed.

Para-dichlor-benzene.—This is an effective moth repellent sold as moth crystals. It may be purchased under its chemical name; trade-marked names for the same material usually imply a higher price. Placed in a closet or hung in a suitable container it slowly volatilizes. Baker (1938) has reported dermatitis in a woman, occurring each time she wore dresses which had been hung in a closet with para-dichlor-benzene. Positive patch reaction was elicited by exposure of the skin to the vapor of para-dichlor-benzene. The material was fastened in the bottom of a pill box which was then inverted over the skin so that there was no direct contact. After dry-cleaning, the clothes were again worn without difficulty.

Derris root. Cubé. Rotenone.—Derris is a genus of tropical shrub comprising about 40 species. It is found practically throughout the tropics including Australia and is more abundant in the Old World than in tropical America. It has long been used by natives as an arrow poison and especially as a fish poison. It is highly toxic for cold-blooded animals and insects but not for man. Natives, therefore, use the root of derris to catch the fish which they then proceed to eat. Haag finds that its reaction is not like that of curare but that it appears to anesthetize nerves and causes death from respiratory failure.

There are four active principles, the chief of which is rotenone.

The insecticidal properties of derris were recognized in 1924. It came into rather wide use especially in powders such as flea powders. Weston (1937) reported two cases of asthma due to such powders. Contact dermatitis has been reported from its use on the skin. It, as other insecticides, has been very largely replaced by DDT.

DDT.—Dichloro-diphenyl-trichloroethane was synthesized by Ziedler in 1784, but its insecticidal properties were not recognized until 1940. During the recent war it was intensively studied and put into wide use. It is now available for household use in various preparations. The powder is stable. It is not water soluble and is usually dispensed in kerosene, polymethyl naphthalenes, xylene, fuel oil or cotton seed oil. It is frequently used as an aerosol. It has not been shown to cause allergic reactions but the solvents most used are irritants and may cause dermatitis and ingestion of sufficient amounts may cause toxic symptoms.

Kapok

Kapok is the fiber obtained from silk-cotton trees, which include several tropical genera of the family *Bombacaceae*. This family is closely allied to the cotton plant (*Gossypium*). Silk-cotton trees are native to Central and South America and the East Indies. They are abundant in the West Indies. The trees are large with handsome mallow-like yellow flowers which appear just before the leaves and are followed by large pods. When mature, these burst open causing the tree to appear covered with glistening white thistledown. The seeds themselves are covered with delicate cottonlike fibers which are carried long distances by the wind. These fibers are too short to be woven into textiles but

are used as stuffing in cushions and upholstery and as a source of buoyancy in life preservers. They are marketed under the name kapok. Most commercial kapok comes from Java.

G. T. Brown states that persons allergic to cottonseed are frequently although not necessarily allergic to kapok. On the other hand, kapok sensitization is practically always accompanied by cottonseed sensitization.

Cohen, Nelson and Reinartz (1934) concluded from their studies that house dust allergen develops in cotton linters under conditions which exclude the possibility of contamination with other common allergens or with bacteria or molds. They state it is probable that the house dust allergen is developed during the ageing process in cotton linters and probably in other substances such as feathers and kapok. Wagner and Rackemann (1937) attempting to confirm these findings, using kapok, found that sterilized kapok does not develop an allergen positive for dust allergies during deterioration except when contaminated with certain specific molds. They find that there are molds having a predilection for kapok as a substrate. The development of the active skin test principle depends upon the growth of molds in the kapok fibers, and skin test activity is directly proportionate to mold growth. This confirms the early pioneer work of Van Leeuwen.

Tobacco

Inhalant allergy to tobacco or tobacco smoke is fairly common. A. Brown records his observed incidence as 1 per cent of asthmatics. This is probably fairly representative of any large group. A much larger proportion give low-grade positive endermal skin reactions, nonspecific, due to natural irritants. Low-grade or borderline reactions should be ignored. Similarly, many with hay fever or asthma may complain of the mechanical irritation of tobacco smoke even though they are not sensitized thereto. In the presence of true sensitization therapeutic desensitization in the writer's experience is usually very satisfactory.

The use of tobacco may cause not only inhalant allergy but contact dermatitis as well. Some persons who develop dermatitis, especially of the upper lip, when smoking cigarettes find that they can avoid this by using cigarette holders. Others must discontinue smoking altogether. I have seen one young woman who develops angioneurotic edema of the lips whenever she touches them with any variety of cigarette. I have seen a young woman allergic to tobacco smoke who develops urticaria when smoking and will manifest hives when she goes into a restaurant where others are smoking, even though she is not.

The wrappers of cheap five-cent cigars usually are stuck together with a gum tragacanth paste. Gum arabic is used in cheap Habana wrappers. Jamaica rum is used in cheap tobaccos. In good Habana there are no additions other than water. Poor grade Habana has a Jamaica rum filler. Nickel cigars often have a glucose syrup paste holding the wrapper. Usually this is corn syrup. The writer has observed a patient, allergic to a number of antigens, who had chronic indigestion as long as he smoked cigars known to have corn syrup in the wrapper. When he changed to more high-grade cigars his indigestion disappeared. Being in the tobacco business he knew the constituents of the cigars.

One should test not only with tobacco extract but with extracts of tobacco smoke. Different grades of pipe tobacco, cigar tobacco and cigarettes may differ in antigenic activity. Many different materials are used to give the characteristic flavor to various brands.

The simplest procedure for making tobacco smoke extract consists in the operator's bubbling exhaled smoke through Coca's fluid which is later sterilized by filtration. An apparatus for sucking smoke through Coca's fluid may be rigged up with a suction pump. The American Tobacco Company has devised a very effective apparatus which employs intermittent suction, thereby burning the cigar or cigarette at the same speed as in the normal process of smoking. (Fig. 53.)

Flaxseed. Linseed

Although flaxseed sensitization is not common it is usually very intense when it does occur. Inhalant allergy due to flaxseed is usually due to hair rinses, chicken feed, some varieties of which contain flaxseed, or to fresh paints and varnishes. Flaxseed asthmatics almost invariably develop severe asthma when exposed to the latter. Indeed, many asthmatics appear to do so even though giving negative skin reactions to flaxseed. It is a safe precaution to advise all asthmatics to avoid exposure to them.

There appears to be some tendency toward crossed reactivity with flaxseed, cottonseed and kapok. Not infrequently persons will react to all three. Tuft states that this group reactivity also involves mustard seed, the legumes and the edible nuts.

Animal Hairs and Danders

Almost every known variety of animal hair, dander or fur has been described as responsible for inhalant allergy. Hyde Salter (1868) mentioned the horse, cat, dog, rabbit, hare, cow, guinea pig and wild beasts. Gould and Pyle (1896) mentioned mice and rats in addition. Walzer (1931) lists horse, cat, dog, goat, rabbit, wool, feathers, cow, hog, camel, mouse, guinea pig, chamois, monkey, muskrat, prairie dog, fox, squirrel, ermine, deer, moose, caribou, "and others too numerous to mention." The three commonest general groups are (1) occupational exposures (horse, cow, chamois fur), (2) pets (cat, dog, monkey), and (3) clothing (rabbit fur, camel hair, goat hair [mohair], seal, etc.). Occasionally the etiologic relationship is hard to trace. An example is the stuffed head of a caribou.

Horse dander.—De Besche (1909) suggested that horse asthma is an anaphylactic phenomenon. While only a small percentage of the allergic population reacts to horse dander, horse asthma is nevertheless one of the commonest manifestations of allergy to animal hairs. In great measure it is an occupational disease, being observed much more frequently among teamsters, stablemen and sportsmen than in other groups. As a rule, sensitization is quite permanent, although there are no statistics on its permanence among those whose occupation enables them to avoid repeated exposure. Desensitization is sometimes reasonably effective. It will be brought out in the chapter on Serum Disease that rapid desensitization of horse asthmatics preparatory to serum therapy is almost universally unsuccessful. The reverse does not hold. Horse asthmatics may be hyposensitized in the treatment of asthma since the urgent need for rapid build-up is not a factor.

Some horse asthmatics, reacting to horse dander, will be found to tolerate horse serum. Others will not. This is because there are two antigens in horse hair, the dander antigen and the serum antigen. One who is allergic to both cannot take horse serum. One allergic only to the dander antigen may be given horse serum. Walker found that 22 per cent of horse asthmatics also reacted to horse serum. De Besche (1937) found likewise.

At times, exposure is quite indirect. The writer observed a horse asthmatic who experienced attacks if her brother who had been riding failed to change his clothes before sitting next to her at dinner. She also developed symptoms when the wind was from the direction of a large stockyard two blocks away. De Besche (1937) described similar cases, such as the wife of a veterinarian. He believes that there may be a volatile factor. He speaks of persons who develop asthma when near a person who "smells horsey." He extracted the characteristically odorous substance of horse urine which he exposed in an uncorked bottle in a room in the presence of asthmatics. The majority of patients so tested developed asthma. He describes several instances of asthma among horse asthmatics due to eating horse flesh. As a rule the horse flesh was a constituent of sausages. I have observed a boy allergic to horse hair who also experienced asthma when exposed to mules.

Cats and dogs.—It is not sufficient for a cat or dog asthmatic to avoid contact with these animals. The animals should be kept out of the house at all times. The writer observed a boy reactive to dog hair who developed persistent asthma after he had moved into another house, the previous occupant of which had had several dogs. De Besche caused a cat to lie on a chair for a time. He then removed the cat and instructed a cat asthmatic to sit in the chair. The patient did not know of the cat but promptly developed asthma. Walker found that 70 per cent of those reacting to cat hair also react to cat serum. Exposure is not always easy to trace, especially in dogs. A huntsman in the writer's experience had asthma only when hunting. He was found allergic to dog hair and it developed that dogs were near him only when hunting. Another huntsman had attacks when hunting and also after opening a closet where he customarily kept his hunting clothes. This man was found allergic to rabbit hair. He had a large pocket in the back of his coat in which he carried game.

Inhalant allergy to rabbits and guinea pigs is not extremely uncommon among laboratory workers.

Castor Bean Dust

There have been at least 50 cases of inhalant sensitization to castor bean dust reported by Arnold, Snell, Figley and Elrod, Vaughan, Bernton, Follweiler, Haley, Bernard and by Bennett and Schwartz.

Thirty were in a single report by Figley and Elrod, occurring in individuals working in a Toledo castor oil mill or living in its neighborhood. Vaughan traced two cases to a Virginia fertilizer factory which used castor bean meal obtained from the Toledo factory. Later he found another case in North Carolina, a boy who handled fertilizer obtained from the Virginia factory. Four of the fifty cases occurred in laboratory workers after repeated exposure. Two were in persons engaged in the handling or transportation of castor beans. The extreme toxicity of castor bean allergen for those sensitized thereto is indicated by the fact that Bennett and Schwartz observed three plus skin reactions following the intracutaneous administration of 1:100,000,000 dilution. Ratner and Gruehl, also Barnard, have demonstrated that the toxic ricin element is in no way related with the allergenic element. Bennett and Schwartz found that an asthmatic extremely reactive to castor bean dust could drink castor oil with impunity.

Miscellaneous

Howard Lee has told the author of an asthmatic working in a match factory whose symptoms were traced to formaldehyde used to harden the tips of matches. Intentional inhalation of fumes of very weak formaldehyde caused an asthmatic paroxysm which lasted nearly three days.

Lee has observed a number of persons who say that their hay fever is worse when using Kleenex. In one such case he made an extract to Kleenex, obtaining positive intracutaneous reaction, with negative controls on nonallergies. We have had a similar case, likewise positive by skin test.*

A man with asthma living in the East reacted to deer hair. Conversation developed, to our surprise, that he had deer as pets. His asthma was relieved after he had disposed of the animals.

A friend of the writer, critical of allergy in general, was found reactive to hog hair. Since he was not a farmer and could see no possible connection this amused him. He later purchased a group of prize hogs. One afternoon, with friends, he got into the pen to show off his prize hogs. He soon developed severe urticaria.

Allergic symptoms occurring only when the subject is hunting need not necessarily be due to pollen, dog hair or game fur. A man had urticaria only during the hunting season and then only after hunting. It developed that this was due to chocolate candy. He eats chocolate only during the hunting season, when he carries chocolate bars and eats them for his lunch.

I have observed a patient who develops asthma when inhaling the fumes from witch hazel.

The Christmas holidays may be the worst time of year for some allergies. A few cases of inhalant allergy to Christmas tree have been reported. A boy reactive to chocolate followed his diet except at Christmas, when he regularly developed asthma from chocolate candy. A man allergic to wheat had a flare-up of dermatitis after eating fruit cake. Some persons experience recurrence of symptoms at this time merely from overeating. A young woman allergic to dust regularly had asthma on Christmas Eve from going to the attic for old Christmas tree decorations. A woman with urticaria due to tomatoes who cooperated none too well in her diet had severe urticaria at Christmas. She had eaten tomatoes. Her philosophy was, "Christmas comes but once a year." At the other extreme an asthmatic child had always had difficulties at Christmas prior to allergic study. The next Christmas her mother stated that it was the first comfortable Christmas the child had ever had.

I make no attempt to enumerate all those allergens which have been reported responsible for inhalant symptoms. The list would be too long. The commoner ones mentioned should be considered in the routine study of every nonpollen inhalant allergic.

*Lee, Howard, Oshkosh, Wisconsin. Personal communication.

PART VIII

BACTERIA

*Living cells are capable of
being trained or educated.
In other words, their be-
havior may be modified by
changed environment.*

—VICTOR C. VAUGHAN

CHAPTER LVI

BACTERIAL ALLERGY AND VACCINES

Here we enter that field which is probably more confused than any other division of the subject.

Experimental

The allergic reaction to bacteria is far more complex than that to exogenous allergens, due in part to the complex structure of bacteria and in part to the response of the host. This is true with dead bacterial vaccines, and is further complicated in the presence of living bacteria growing within the body.

In bacterial allergy we shall see a differentiation into two distinct phases. Each has been extensively studied and each has surprisingly enough been given a distinctive terminology to which very few have taken exception.

Bacterial Anaphylaxis

Anaphylaxis of the experimental type, similar to that of the guinea pig to egg white or horse serum, was demonstrated very early by Rosenau and Anderson (1907), and confirmed by others. These authors found that dead colon, anthrax, typhoid and tubercle bacilli could sensitize and, on reinjection, produce anaphylactic shock. Vaughan and Wheeler confirmed these observations and showed that with these proteins, as with egg white and horse serum, the whole antigen can be split into moieties, one of which will sensitize, while the other produces shock but does not sensitize. Refinements in the production of protein split products have more recently confirmed the existence of two moieties, not identical with those of Vaughan and Wheeler, and have demonstrated their allergenic significance.

True bacterial anaphylaxis has been shown by (1) classical shock in the sensitized animal, (2) passive transfer and (3) positive reactions in the Dale uterine strip technic. None of these is accomplished as easily with bacteria as with egg white or serum. The more complex nature of the bacterial antigen has been shown by a number of observers, the more striking contributions being as follows:

Residue antigen.—Zinsser (1923) separated tubercle germ substance into two moieties, a nucleoprotein and a nonprotein which he termed *residue antigen*. He showed that while the former caused antibody production, the latter did

not. With antibodies once formed, the latter was capable of uniting to cause shock. He concluded that his residue antigen was a hapten, comparable to those previously described by Landsteiner for drugs.

Specific carbohydrate.—Heidelberger and Avery demonstrated similar fractions in the pneumococcus, a group-specific protein and a type-specific soluble carbohydrate. They showed that immunologically the protein was specific for all pneumococci and could produce sensitization, either alone or combined with the type-specific carbohydrate. The latter was incapable of producing sensitization, but, once the sensitized state had been produced either by the protein or by the combined protein and carbohydrate, it could produce shock. The residue antigen of Zinsser and the specific carbohydrate of Avery produce no antibodies, but if antibodies exist they will combine with them to produce anaphylaxis. This is analogous to the situation in allergy to aspirin, quinine and other nonprotein drugs. We may look upon the soluble specific substance as hapten. Avery and his collaborators have confirmed this hypothesis by showing that a chemically pure sugar radicle may be attached to a simple serum globulin to form a new protein complex with biologic specificity of its own.

Denaturization.—Early positive skin reactions of the wheal and erythema type to tubercle bacillus substance are not observed, but are seen with pneumococcus substance and with pneumococcus carbohydrate, a fact which suggests to Zinsser that its absence in the former case is due to difficulties in extraction of the antigen. Pneumococcus antigen may be obtained by a simple process of autolysis, while tubercle antigen receives much more intensive chemical treatment. This suggests that much of our difficulty in the study of clinical bacterial allergy with vaccines, is due to the denaturizing effect of manipulation.

Bacterial anaphylaxis as described above is an interesting laboratory phenomenon, but one with which we rarely have to deal in clinical medicine. Clinical studies deal more with bacterial allergy.

Bacterial Allergy of the Tuberculin Type

Pirquet (1907) described a delayed reaction following skin testing with tuberculin—erythema, induration and occasionally even necrosis developing after 24 to 48 hours. This is characteristically present in tuberculous persons and animals, but is absent in the nontuberculous. In view of its specificity he considered this reaction allergic. Confirmation is found in that the tuberculin reaction requires an incubation period of from 7 to 10 days after infection of the animal, before it will respond positively.

Immunologists have assumed that this reaction is basically different from the prompt positive to extrinsic allergens; that it depends on an interaction between the host and the invading organism. We shall see that there may be a common basis for the delayed tuberculin type reaction and the delayed extrinsic allergen reaction, but for the moment our interest is in tracing the historical development of the more generally accepted concepts of today.

Third factor—tissue reaction. Baldwin (1910) presented evidence that skin sensitization of the tuberculin type does not occur in the absence of active infection within the living organism. The conclusion was that the tuberculin reaction depends either upon liberation of a toxin or other secretion from the living organisms, or upon inflammatory tissue reaction in the tubercle.

Baldwin further showed that animals artificially sensitized to tubercle germ substance did not give the typical tuberculin skin reaction. The two conditions appear to be different, the latter dependent upon the presence of tissue reactions against the organism.

Zinsser and Petroff later showed (1924) that dead tubercle bacilli could produce tuberculin sensitiveness, provided tubercle was formed in the tissues following injection. This fact removed metabolic activity on the part of the bacteria from consideration and gave further substantiation to the assumption that tuberculin sensitization depends upon the inflammatory tissue reaction, the tubercle.

The observations of Dienes give further substantiation of the specificity of the delayed tuberculin reaction modified by the tissue responses of the host. When egg white was injected into tuberculous lesions of guinea pigs, skin sensitization to egg could be demonstrated after seven days, but in this case it took on the form of a delayed response indistinguishable from the tuberculin reaction. Nontuberculous guinea pigs similarly treated with egg white showed the early type of skin reaction. Dienes' observation suggests that the tissue cells involved in the tuberculous lesion in some way determine the nature of the subsequent skin reaction.

Zinsser summarizes his discussion of the significance of the tuberculin reaction with the following points:

(a) Since the tuberculin and similar reactions are specific, one must assume that the excitant or stimulating substance emanates from the bacteria.

(b) Since the skin reaction may become positive after injection of dead bacilli, a soluble toxin or other substance produced by living organisms is excluded as a necessary factor.

(c) Since allergy, indicated by the skin reaction, develops only when there has been a tissue reaction around the injected organisms, the action of the inflammatory tissue, possibly its enzymes, is required for the liberation of the sensitizing antigen from the bacteria.¹

(d) The fact that tuberculin, injected into a nontuberculous pig, will not sensitize the animal suggests that in the manufacture of tuberculin the antigenic substance is destroyed. This substance is formed or liberated more gently and with less damage by the action of the inflammatory tissues upon the bacteria.

(e) With organisms such as the pneumococcus, from which the nucleoprotein fraction may be obtained *in vitro* without such extensive chemical treatment, tuberculin type reactions may be induced following vaccination. Here, the intervention of tissue reaction is unnecessary.

Summarizing, bacterial allergy is a specific hypersensitiveness to antigenic material of the nucleoprotein type, discharged into the body from infected foci. It is liberated from the latter by inflammatory tissue reaction. Failure to produce sensitization of the tuberculin type by injections of tuberculin is due to the violence of the chemical manipulation required to get the antigenic substance into solution.

There is no passive transfer of tuberculin allergy.

Shwartzman phenomenon of local tissue reactivity.—Shwartzman (1928) described a curious phenomenon of local tissue reactivity to bacterial filtrates. A filtrate, free from autolytic products, was injected into the skin of a rabbit. Twenty-four hours later the same filtrate was administered intravenously. Within four or more hours after the second injection a sharply circumscribed

inflammatory area with hemorrhage and at times, necrosis, appeared at the site of first injection. The *skin-preparatory* injection produces no local manifestation until after a second intravenous or *reacting* injection is given. The local skin susceptibility to injury by this procedure is only temporary, disappearing after 48 hours.

The phenomenon has been produced in rabbits, goats, horses, guinea pigs. There is evidence that it may occur not only in the skin but also in internal organs such as stomach, kidney, liver, peritoneum, intestines, testes, joints and sarcomatous tissue. Only certain bacteria have been shown to produce it. These include the typhoid-dysentery group, cholera vibrio, pneumococcus, gonococcus, meningococcus, streptococcus, influenza bacillus, pertussis bacillus, the bacillus of hemorrhagic septicemia. *Leptothrix*, certain viruses and certain malignant tumors have done likewise.

No strict specificity has been observed, since if any one of the above is used as the preparing factor, either it or any of the others may be used as the reacting factor.

There is evidence of an immunity response, or increased tolerance, since horses may be immunized against the phenomenon. Such immune horse serum neutralizes the preparatory or reacting substance, thereby preventing the phenomenon. This procedure may possibly lead to the development of new therapeutic sera.

Relationship to anaphylaxis.—Evidence has been presented, especially by Gratia and Linz, suggesting that the Schwartzman phenomenon is allied to anaphylaxis. Schwartzman (1937), however, has presented convincing reasons why the two are not related. These include (1) absence of specificity in the relationship between the preparatory and provocative factors; (2) failure to elicit passive transfer or specific desensitization; (3) the shortness of incubation period (a few hours); (4) the fact that the state of reactivity is induced by a single first injection; (5) the failure of animal proteins to produce a similar phenomenon. Certain blood changes such as leukopenia and delayed coagulation suggest similarity to anaphylaxis, but are due merely to the introduction of bacterial filtrate into the general circulation. In histologic appearance there are distinct differences between the Arthus phenomenon and the Schwartzman phenomenon.

Schwartzman does believe that there may be some connection between the phenomenon and that of bacterial allergy of the tuberculin type. In this case the skin test represents the *preparatory* factor, while substances secreted into the blood from the focus of infection (tubercle or other infective focus), contribute the *reacting* factor.

The evidence is by no means conclusive. Although the phenomenon is often mentioned in discussions of bacterial allergy, there is rather more evidence that it is a toxin phenomenon. In last analysis there is as yet no explanation of its mechanism or significance.

Allergy in rheumatism. Haptens have been produced with organisms other than tubercle bacillus and pneumococcus. These include *Bacillus lactis aerogenus*, pneumobacillus, yeast and streptococcus. Tuberculin type reactions have been obtained with extracts of tubercle bacillus, *B. mallei*, *Brucella abortus*, *Brucella melitensis*, gonococcus, *Treponema pallidum*, *Streptococcus scarlatinae*, *Streptococcus hemolyticus*.

A number of investigators have studied a possible bacterial allergic factor in rheumatic fever and atrophic arthritis. The joint manifestations of rheumatism usually occur without local infection, thus suggesting an allergic

or kindred reaction. Swift and Kinsella (1919) demonstrated that no single streptococcus is responsible. The idea of a number of potential excitants, with but a single type of tissue response, again fits into the conception of allergy. Most organisms isolated from rheumatic cases are of the *Streptococcus viridans* group, which latter manifest a strong tendency to develop chronic foci in man. However, they are not bacteriologically or serologically identical. Although such streptococcal foci are found in many rheumatic cases, positive blood cultures and positive joint cultures are rare. Joint lesions may be produced in animals with extracts of these organisms.

Swift states, “. . . the so-called allergic theory does not establish unequivocally the etiological relation of streptococci to rheumatic fever, but only furnishes us with the best explanation of how different strains can all induce a similar clinical and microscopic picture.”

Indirect evidence suggesting an allergic factor in atrophic arthritis is contributed by the observations of Crowe, Small, Frieberg, Dorst, Vaughan, and others, on the need for extremely small dosage in vaccine treatment, following in general the principle of coseasonal pollen therapy.

Significance of the delayed reaction.—The delayed or tuberculin type reaction is especially characteristic of bacterial allergy and appears to be specific within rather narrow limits. The suggestion has been made that the absence of the early skin reaction may be due to defects in our methods of preparing the antigen. With those bacteria in which simpler methods are used early reactions have been observed. In routine skin testing with stock and autogenous vaccines, the delayed reaction is a characteristic positive finding, but early or half-hour responses are seen in my experience in from 5 to 10 per cent of tests.

We should also bear in mind that delayed positive reactions are observed in routine testing with extrinsic atopens, foods, pollens and other inhalants. The writer attaches more significance to these following the scratch test than following endermal testing, since in the latter an uncertain proportion may be nonspecific, due to chemical irritation by constituents of the extract. In the earlier discussion of the delayed reaction (Chapter XIX) the author suggested that this might well be a specific reaction, less explosive in nature, due to the fact that at the time of testing the patient was in more or less constant or chronic contact with the allergen. In bacterial allergy with chronic foci of infection, this would be definitely the case and if the concept is correct, one would expect the reaction to be less explosive.

For the present this cannot be accepted as more than a suggestion. It is safer to accept the general conclusion of bacteriologists, that the reaction is dependent upon a “third factor” besides antigen and antibody, the factor of tissue activity. Even this is no adequate explanation, since the tissue factor still remains incompletely explained. However, the following recent investigations might be reviewed in connection with the writer's suggestion.

Development of sensitization. Dienes has observed that repeated intracutaneous injections of foreign serum and egg in guinea pigs caused gradual evolution of delayed, tuberculin type reactions. With further injections, the immediate or wheal type reaction gradually evolved. Jones and Mote observed a similar evolution of skin sensitization, from the delayed tuberculin type to the prompt wheal, following repeated injections of rabbit protein into the skin of man. Simon and Rackemann confirmed these latter observations, using guinea pig serum. Injections were given at weekly intervals to persons suffering from respiratory allergy and to others, used as controls, who

gave no history of allergy. The evolution of the positive skin reaction was similar in both groups, again showing confirmatory evidence of no qualitative difference between the allergic and the nonallergic. Both groups were susceptible to artificial sensitization of the skin with guinea pig serum, the degree of sensitization being light or early when the tuberculin type reaction was obtained and strong when the wheal type was observed. It is also interesting in this connection that passive transfer was not accomplished at that stage in the development of sensitization represented by the tuberculin type reaction. Passive transfer was accomplished when whealing occurred. It should be recalled that tuberculin type sensitization cannot be transferred passively.

The findings strongly suggest that both the anaphylactic and the tuberculin types of allergy have a common basis and that one factor which determines which type exists, is the abundance or otherwise of antibodies or reagins in the blood.

Simon and Rackemann also sensitized the skin of atopic individuals to guinea pig serum following intranasal application. Nasal mucosal response was similar to the objective response in the skin. The first application caused no symptoms. Subsequent applications, early, caused delayed allergic coryza commencing after 24 hours and lasting several days. Later applications caused immediate nasal symptoms. Several weeks were required for this.

Bacterial allergy and immunity.—At several points in this volume we have spoken of the apparent close relationship between immunity or adequate protection and allergy or inadequate or disorganized protection. Nowhere has this been more comprehensively studied than in bacterial allergy. The concept developed almost with the beginning of the study of anaphylaxis. Otto, one of the first investigators, formulated the picture of the anaphylactic response based upon the Ehrlich side-chain theory of immunity. Doerr even included immunity in his classification of states of altered reactivity which were grouped under the heading, Allergy. It is quite true that in many of the reactions to infection, it is difficult to determine whether we are dealing with one that should be designated allergic or immune.

For example, the following explanation of the immunologic mechanism that develops in the course of typhoid fever has always been attractive. During the incubation period, the antigen, the typhoid bacillus, proliferates in the blood without causing symptoms. This phase is analogous to the first or sensitizing injection of an antigen and gradually calls forth antibodies. By the time sufficient of the latter have accumulated, and sufficient antigen is constantly being destroyed, symptoms of disease appear. Convalescence represents that period at which the antigen has been destroyed or sequestered. Symptoms are not explosive as in anaphylactic shock, because the process is a gradual one. If, following recovery, the living antigen again enters the body, it is promptly destroyed through its combination with antibodies, before it has an opportunity to multiply. Now, according to the theory, this is precisely the mechanism which is responsible for the development of sensitization to pollens or foods. In the latter case, once sensitization has developed, reexposure usually involves the sudden entrance of such a large quantity of excitant that symptoms result. In this theory allergy and immunity have a common basis, but there are many points that have never been established and we must conclude that the theory is but a stepping stone to a more adequate one which unfortunately has not yet been found. Rich has concluded that bacterial allergy and immunity may be entirely independent.

Pagel (1938) like Rich finds that the phenomena of tuberculin allergy and immunity to tuberculosis may appear independently but considers the two as different degrees of the same allergic response. "Immunity without hypersensitiveness indicates a higher degree of antibody production and thereby of tissue activity than immunity following hypersensitiveness."

Does the delayed reaction represent a protective response? Seegal and Seegal have summarized the present rather confused state of information.

(a) First, bacterial allergy of the tuberculin type may exist against *organisms which are not causing disease* in the individual case. Filtrates from bacteria of the upper respiratory tract may produce skin reactions in healthy individuals. Filtrates or vaccines from *Streptococcus viridans*, *hemolyticus* and *nonhemolyticus*, may produce positive skin reactions in normal individuals. This may indicate previous subclinical infection.

(b) Bacterial allergy (tuberculin type) to the organism causing a disease may occur during the course of a disease *without any obvious relation to prognosis*. The positive skin reaction appears to be but an associated phenomenon in the infection. This is especially noteworthy in parasitic diseases such as trichinosis, echinococcus infection, ascariasis, glanders and infectious abortion of cattle.

(c) In other circumstances, allergy as evidenced by the delayed positive skin reaction may appear to *exert a beneficial effect* in the course of an infectious disease. This has been studied most extensively in tuberculosis. Children who have not yet developed a positive tuberculin reaction usually become rapidly worse when actively infected with tuberculosis. Adults giving positive tuberculin reactions run a much milder course if infected. Adults, such as nurses in a tuberculosis sanatorium, who fail to give positive tuberculin reactions, appear to be much more susceptible to active infection than those who are tuberculin positive. Experimental confirmatory evidence is found in the Koch phenomenon (1891). Inoculation of the skin of a nontuberculous guinea pig resulted in extensive local infection, while that of a pig already infected and giving a positive tuberculin reaction resulted in a rapid local necrosis with subsequent local healing. This did not beneficially affect the outcome of the preexisting systemic tuberculous infection.

(d) Allergy to the causative organism as indicated by the tuberculin type skin reaction may *exert a harmful influence on the course of the disease*. This is illustrated in arthritis, if we assume that the joint manifestations are allergic. It is also seen in the results of tuberculin administration in tuberculosis.

Obviously the problem of bacterial allergy is a much more complicated one than that of extrinsic or atopic allergy. Nevertheless, there is much to suggest a common basis.

The Burky phenomenon.—The possible action of a bacterial toxin in fostering the production of the allergic state is an interesting study.

Burky observed that in the process of *immunizing* rabbits to staphylococcus toxin, they became *sensitized* to the broth in which the toxin was produced. Proceeding on the theory that a broth hapten was attached to the toxin, he attempted to produce sensitization to other substances. The protein of the crystalline lens is organ specific, apparently identical in all animals and different from the somatic protein of the animal. Attempts to sensitize animals to lens protein have heretofore been unsuccessful. Burky grew toxin-producing staphylococcus in a culture medium containing lens protein. Following injec-

tion of this lens-toxin combination into animals, he produced sensitization to the protein of crystalline lens. He next accomplished the same with rabbit muscle protein, sensitizing rabbits to their own muscle.

Of especial interest to ophthalmologists is the fact that rabbits which had been thus sensitized to lens protein developed typical endophthalmitis on injection of lens protein into the anterior chamber of the eye. This is sometimes seen in persons who have been subjected to cataract operation, and it has been presumed that they have become allergic to lens protein.

The clinical condition was described in 1922 by Verhoeff and Lemoine who proposed the name endophthalmitis phaco-anaphylactica. Until the work of Burky it had not been reproduced experimentally, although Courtney has shown positive skin reactions to lens protein in persons who have experienced this form of ophthalmitis following lens extraction. Courtney tested his patients intracutaneously prior to lens extraction and desensitized those who gave positive reactions. With this preoperative treatment, he reduced the incidence of endophthalmitis.

It is difficult to sensitize rabbits to ragweed. Using the same methods, Burky had no difficulty in apparently sensitizing rabbits so that they experienced anaphylactic reaction following the inhalation of ragweed pollen.

Significance.—There are two points in the practical application of this phenomenon. First, it seems possible that an individual might become allergic to some of his own tissues as a result of the activity of staphylococcus toxin or other toxin elaborated in a focus of infection. The individual might become sensitized to some element of the infected tissue. The important point in this connection, as regards bacterial allergy, is that the customary testing with any number of pure culture bacterial vaccines might be negative in spite of the fact that the toxin of one of these bacteria might have been the responsible sensitizing factor.

The second point made by Burky is that an animal previously sensitized in this way to certain substances in his own tissues might react to the liberation of such substances following trauma, etc. Thus, rabbits that had been sensitized to rabbit muscle-toxin antigen, so that they reacted positively following reinjection of this or of rabbit muscle alone, were found to react likewise to simple muscle trauma such as pinching with hemostats.

The reactions appear to be specific in that an animal sensitized to lens protein does not react to autogenous muscle protein and vice versa.

This observation that staphylococcus toxin alters the antigenicity of ordinarily inert substances and appears to increase so-called normal antigenicity, opens a new field in allergic study. Previous studies by Rosenau and Hooker with diphtheria toxin, showing that toxin-antitoxin serum mixtures produce higher sensitization to horse serum than does horse serum alone, point in the same direction, suggesting that this may be a characteristic of toxins in general.

Swift and Schultz have confirmed Burky's observation with other proteins and bacterial toxins. Burky had found that if one injects toxin in one site and lens protein in another, sensitization to the latter occurred in about one of four animals. Swift and Schultz likewise found that sensitization could be produced when toxin and protein were introduced, either into the same tissue with an interval of several hours between injections, or into different veins. They found a similar "synergic conditioning" when horse serum and diphtheria toxin or streptococcus toxin were used.

Haptens and Bacterial Allergy

Recent studies have produced abundant evidence that a combination of allergen with some nonallergenic substance may result in a much more potent or more highly antigenic allergen. Early hapten investigations dealt with the combination of nonallergenic chemicals such as iodine, iodoform or quinine, with protein. Almost any protein would do, since the antigenic specificity appears to lie with the nonprotein radicle or hapten. The theory of a combination with human protein after penetration into the body appeared to explain drug idiosyncrasy. Here it was only the hapten which entered the body, the protein-hapten combination being produced following penetration.

In bacterial allergy we have again seen evidence of hapten activity. Here, however, we are dealing with a hapten-protein combination already formed before penetration. Even so, the concept of antigenic specificity remains, in great measure. *Pneumococcus* protein is responsible for the specificity of sensitization within the group of pneumococci, but the carbohydrate hapten attached to this protein determines type specificity within the pneumococcus group.

Avery and Goebel have found that when two chemically different carbohydrates are bound to identical proteins, the newly formed antigens are immunologically different. When one carbohydrate is conjugated with two different proteins, both of the new proteins appear serologically alike. The carbohydrates or glucosides alone are not precipitated in immune serum but when present, they do inhibit precipitation of the sugar-protein antigen in such serum. The glucoside if administered prior to injection of the glucoside-protein combination will inhibit shock from the latter. This protective action of the glucoside disappears after two hours. The glucoside or carbohydrate must, of course, be identical with that which is present in the sugar-protein combination. The inhibitive effect is, therefore, specific.

This is similar to what we have seen in the discussion of tubercle bacillus sensitization, where sensitization could be produced only with the sugar-protein combination; but such sensitization having once been produced, the sugar fraction could produce anaphylactic response.

Here, then, we find the situation quite analogous to that in drug allergy in which only the hapten penetrates the body. And here again one might hypothesize a combination of bacterial hapten or carbohydrate with body protein. This, also, brings us back to the Burky phenomenon in which the hapten appears to be staphylotoxin. If such toxins are secreted by organisms in foci of infection one must realize that in the clinical allergies focal infection may eventually be shown to play a part which is specific rather than nonspecific.

There is one point of difference between drug and bacterial haptens. While the latter may produce positive skin reactions, the former usually do not. The writer does not consider this difference fundamental, especially in view of the fact that so many differences which have appeared fundamental have in time been reconciled.

Haptens and atopic allergy. There is increasing evidence suggesting that haptens may play a part in atopy, that form of allergy which has heretofore been considered more nearly the clinical analogue of classical protein anaphylaxis.

Pollen haptens.—Although the pollen antigen has been usually considered to be protein, those who have found fractions which are polysaccharide in character suggest that these fractions may act as haptens. So long as findings are so at variance as they are up to the present, it is not possible to say whether haptens are of importance in pollen sensitization.

Dust and foods.—Grove and Coca concluded that the active substance in dust, as in pollen, is nonprotein. By contrast, they concluded that the excitant in peas and horse serum is protein. This raises a fundamental question on which much work remains to be done. The striking early experimental work dealt with the classical phenomena of protein sensitization and the whole field of clinical allergy has been evolved on the basis of this interpretation. The hapten concept came later and it is decidedly more recently that its great importance and wide applicability have been recognized. The question now arises whether some as yet undetermined hapten plays its part even in ordinary protein allergy, such as experimental anaphylactic sensitization or clinical sensitization to horse serum, egg white, etc. There is as yet no answer to this question, and it seems safer for the present to assume that allergy exists to proteins alone as well as to protein-nonprotein complexes.

One additional observation suggests the possibility of hapten activity in simple protein sensitization:

Thiers and Chevalier, in a clinical study, found that allergenic food, such as milk, still gave positive skin reactions following intragastric digestion, ultrafiltration and neutralization and that hyposensitization with these digestion filtrates relieved symptoms. Presumably, all protein had been removed. This observation is of interest in connection with Walzer's work on enteral absorption, and suggests that if food protein is broken down prior to absorption, hapten might be responsible for the positive observations.

Clinical Bacterial Allergy

Theoretically, one would anticipate that bacterial sensitization may cause some of the common allergic symptoms. Investigation has, on the whole, been disappointing. Some investigators, notably, Thomas, Famulener and Touart, and G. T. Brown, believe in the specificity of bacterial sensitization, especially in respiratory allergy, but the majority feel that the point is not yet proved.

Difficulties.—One possible reason for failure has been the difficulty of making vaccines or bacterial extracts in which the test substance is identical with the organism removed from the focus. In bacterial anaphylaxis animals were sensitized with substances which had been grown artificially, and were shocked following reinjection of the same material. This is a different process from that of obtaining the presumptive antigen from a source of infection in the body, growing it on artificial media, and killing it with heat or chemicals. The test material can scarcely be considered identical with the original. Sterilization by grinding in a ball mill until each individual bacterium is disrupted should prevent the denaturization that presumably accompanies heat or chemical treatment, but even so the character of the culture medium may cause some alteration in antigenicity. It has been found, for example,* that typhoid vaccine grown on a protein-rich medium is more likely to produce chill and fever when given intravenously than one which is prepared on protein-poor medium. There is evidence in food allergy that the nutritive source

*Brown, George E. Personal communication.

may cause sufficient alteration to change allergenic activity. Thus, Kern* has described a patient who has symptoms after eating Michigan celery but can eat celery grown elsewhere with impunity. The writer has a patient who can eat Colorado celery but not Michigan celery. This same person can eat California oranges but not Florida oranges. Another cannot eat California oranges but has no symptoms from Florida oranges.

It would appear that the most nearly ideal vaccine should be one which is sterilized in a ball mill and grown on a medium which contains human blood as the chief nutritive ingredient. The desirability of human blood has been emphasized by Famulener.

Wells has emphasized the ease with which antigenic proteins may be denaturized. Heat-killed tubercle bacilli injected into guinea pigs produce the tuberculin type of allergy. Extract of ground tubercle bacilli, on the other hand, produces a different type of sensitization, such that subsequent skin testing with tuberculin produces an immediate wheal with erythema; very rarely a tuberculin type delayed reaction.

If the importance of haptens is as great as recent evidence would suggest, we might conclude that a vaccine which fails to give an early positive reaction has been denaturized in its preparation. This would be the case with nearly all vaccine preparations now in use. If this assumption should be proved correct, then the conclusion is obvious that until methods of vaccine preparation have been improved, progress in the study of bacterial allergy will be slow.

Early vs. late reactions.—The consensus of those who have attempted clinical testing with bacteria is that the delayed positive reaction is the type characteristically observed but that very occasionally an early wheal reaction is seen. Our own experience is that the occasional finding of an early wheal does not necessarily indicate that the vaccine is an unusually good one, little denaturized, because using the same vaccine on successive patients, we find that the whealing is not constant for all persons tested. Of course, it may be that it is constant with the particular vaccine, for all who happen to be allergic to the specific bacterium, but it is also possible that the factor of degree of sensitization of the individual being tested plays a part. Although I have made no statistical analysis, my impression has been that vaccine treatment of patients giving the wheal type reaction has been generally more successful than vaccine treatment based upon the delayed or tuberculin type reaction.

In general, I would say that the early reaction is more specific in bacterial allergy just as it is in atopic allergy and that every effort should be made to develop vaccines capable of producing this type of response. Forman has expressed the same belief. He finds atopic bacterial asthma common, especially to *Staphylococcus albus* and *aureus*, *Streptococcus viridans* and *hemolyticus*, *Pneumococcus*, *B. coli* and the Friedländer bacillus. With these, he produces not only an early wheal, but also passive transfer. He stresses the difference between bacterial atopy and bacterial allergy and recommends treatment based upon the former. Smith† reports numerous cases with wheal reaction to autogenous vaccines, some of whom were entirely relieved following vaccine treatment. Up to the present, however, nearly all the studies of clinical bacterial allergy have been based upon the delayed reaction, the fact of possible early reactions being mentioned only as an incidental observation. True, the evidence is that the delayed reaction is also specific, but therapeutic results should be better with a vaccine which will give a wheal reaction.

*Kern, Richard A., Philadelphia. Personal communication.

†Smith, David T., Duke University. Personal communication.

Stevens and Jordani (1937) find immediate bacterial reactions occurring particularly in hay fever and asthma.

The ensuing discussion will follow the more prevalent concepts of present-day practice.

Testing with bacterial antigens.—Although a number of workers have written on the subject, Thomas, Famulener and Touart and Brown have been the most enthusiastic advocates of specific bacterial desensitization. Thomas and Touart (1924) reported treatment of 200 bacterial asthmatics, with complete or nearly complete relief in 65 per cent. The offending organisms included staphylococci, streptococci and pneumococci, chromogenic cocci, enterococci, *B. coli*, *B. Friedländer*, *B. fecalis*, *Alkaligenes*, *Micrococcus catarrhalis* and atypical gram negative cocci and bacilli.

These authors give chief attention to the character of the delayed positive reaction. Thomas states, "The mistaken attempt to gauge their significance from their early, or half-hour appearance, has been the cause of needless failures in the hands of some operators who have not sensed the significance of the late reaction. Early wheals are obtained in but a small percentage of cases, but the results of treatment as determined by late vaccine reactions have demonstrated their significance also." He reports 35 early positive reactions, approximately 25 per cent, among 134 asthma and hay fever patients. In evaluating the delayed reaction these authors enumerate the following features, the later ones being present as a rule only in severe reactions: (1) an indurated slightly elevated nodule; (2) redness of the skin over the nodule; (3) the surrounding zone of erythema, the areola; (4) tenderness on pressure; (5) local heat; (6) lymphangitis with or without local sterile pustule and regional lymphadenopathy; (7) fever and malaise; (8) pustules. The severity of the reaction is recorded in terms of these features for successive days, until all local manifestations have disappeared.

TABLE XLVIII.—CLINICAL REACTIONS TO INTRADERMAL INJECTIONS OF VACCINES

NAME OF REACTION	DESCRIPTION	SIGNIFICANCE
Early local reaction	Urticarial wheal occurring within ½ hour at injection site	Presence of bacterial atopy
Late local reaction	Macular or papular lesion at injection site, at its height at end of 48 hours	Presence of bacterial allergy
General toxic reaction	Malaise, prostration, fever, etc.	Systemic response to specific or nonspecific toxins
Symptomatic reaction	Onset or increase of original allergic symptoms	Presence of bacterial allergy
Relief reaction	Temporary relief from original allergic symptoms	Presence of bacterial allergy
Focal reaction	Lighting up of symptoms of infection at site from which vaccine organisms were obtained	Harmfulness of focus to patient
Recurrent local reaction	Reappearance of a faded late local reaction	Undetermined
Negative reaction	Absence of response to vaccine injection	Absence of bacterial atopy or of bacterial allergy; harmfulness of vaccine organisms to their host

They provide the accompanying table (Table XLVIII) for the interpretation of reactions. They believe the 48-hour reading the most important. The reaction, depending upon its severity, displays any or all of the 14 phenomena listed in Table XLIX.

TABLE XLIX.—FEATURES OF THE LATE VACCINE SKIN REACTION

1. Nodule	8. Lymphangitis
2. Redness	9. Pruritus
3. Areola	10. Ecchymosis
4. Swelling	11. Pustule
5. Tenderness	12. Eosinophilia
6. Pain	13. Desquamation
7. Heat	14. Pigmentation

They record the intensity of the reaction on successive days with a code in which the initial letter of each feature of the reaction indicates the presence of that feature and its size, or intensity. A nodule of 0.3 centimeter or less in diameter is recorded as N. If larger it is NN. An areola 1 centimeter broad is recorded as A. An additional A is added for each increase of 1 centimeter.

“A reaction consisting of a small tender nodule, redness, heat, and an areola 1 centimeter in diameter is recorded as NRIITA. Should the areola be 3 centimeters broad the above reaction would be expressed as NRHTAAA.”

They regard as positive a reaction which after 48 hours presents more than 3 of the features characteristic of the reaction, provided none of these are present in the control. If some are, these must be outnumbered by a total of three in the reaction site. An apparently positive reaction which disappears before 48 hours is considered nonspecific and negative.

Specificity.—In substantiation of their claim that bacterial allergy is specific they present the following points. A positive reaction is constantly or consistently so on repeated testing until modified by repeated desensitizing injections. The positive late reaction is often accompanied by an increase in allergic symptoms. Positive reactions sometimes give temporary relief. During the course of treatment, the intensity of the delayed positive diminishes parallel with improvement in symptoms. Eosinophilia has been shown in the late positive reaction, an eosinophile count higher than that in the systemic circulation. Seventy-one per cent of 300 asthmatics treated with autogenous vaccine were relieved over periods of from 3 months to 10 years. In the preparation of vaccines Famulener recommends direct plating on human blood agar with subsequent cultures in special media, especially blood dextrose broth.

Clinical routine.—Grafton T. Brown believes that bacterial allergy can be fairly readily diagnosed by clinical methods. His discussions deal chiefly with allergy to bacteria in the respiratory tract.

A history of onset after age forty, seasonal exacerbation during the winter months with some irregularity in the seasonal incidence and the history of more than the usual amount of cough and expectoration are suggestive. “It might be said that the bacterial asthmatic coughed himself into the attack whereas the atopic asthmatic coughed himself out.”

In bacterial asthma the attacks more commonly begin in the early morning while in atopic asthma they occur at any time, without warning. In the latter, onset is usually more abrupt.

Bacterial asthmatics are more subject to colds, sinus trouble and bronchitis. In seasonal hay fever, itching of the eyes indicates exogenous rather than bacterial etiology. In bacterial asthma the nasal secretion and sputum are likely to be thick, sticky, yellowish, purulent. Examination shows a red, inflamed, congested nasal mucosa often with polyps and with inflammation about the sinus orifices, where pus often exudes.

It will be seen that Brown's description of the clinical picture in bacterial allergy is that of infection. It should be borne in mind that not all asthmatics with accompanying respiratory tract infection are necessarily allergic to bacteria. Brown also emphasizes that bacteria in remote sources of infection should be isolated and used in testing. He uses stock and autogenous vaccines.

For treatment the vaccines giving positive delayed reactions are preferred. Initial dosage is usually 0.1 cc. of a suspension containing 50,000,000 bacteria per cc. Injections are given not oftener than every five days. When top dosage is reached, represented by 1 cc. of a concentration of 5,000 million organisms per cc., the interval between injections is extended.

Brown feels that better results are obtained when the injections are followed by local subcutaneous reaction. The intensity of this reaction determines the interval between injections and the size of succeeding doses. He describes one constitutional reaction which is peculiar to vaccines, taking the form of a chill, fever, malaise and generalized aching, simulating grippe or influenza. He attributes this to accidental entry into a vein and cautions against this. The customary precaution consists in tugging on the barrel of the syringe to see if blood returns prior to injection. Benson (1923) reports as good relief from vaccines based on skin tests in bacterial allergy as he obtained with exogenous extracts in extrinsic allergy.

Standardization. The standardization of vaccines described by Thomas, Touart and Famulener is based upon the method of Hopkins. Using a Hopkins centrifuge tube, 1 per cent suspension of physiologic saline is prepared, following which the bacteria are killed by heat. The initial therapeutic dose is usually 0.05 cc. Injections are given at three- to five-day intervals. If improvement follows this dose, it is kept steady. If not, it is increased by a like amount each time. As symptoms improve, the interval is increased to weekly, biweekly or even monthly injections. This may be continued for several months.

Autogenous vs. stock vaccine. Cooke likewise prefers autogenous vaccines. He, however, finds specific skin tests with vaccines to be of no aid. Immediate reactions rarely occur and when they do they are, in his opinion, of no clinical significance. The delayed positive may occur with a vaccine which does not produce asthma, while the vaccine with negative skin reaction may cause attacks. Cooke believes the symptomatic reaction, an asthmatic attack following use of a vaccine, is the only accurate criterion at present as to the allergenic capability of the vaccine. He prefers those autogenous vaccines which produce symptomatic asthma. He has seen good results from vaccine therapy, although, as he states, the effect of this treatment is hard to evaluate. Very occasionally an individual appears to be strongly allergic to the bacterial allergen. He describes a symptomatic reaction to a dose as small as 0.0001 cc. of 1 per cent suspension. My own experience with vaccines is comparable with that of Cooke. The selection of the proper vaccine is not based on whether it is a stock or autogenous vaccine. Many a time I have failed to benefit with one autogenous vaccine and obtained satisfactory results

with another, obtained in pure culture at the same time. The presence or absence of positive immediate or delayed reaction to a stock or autogenous vaccine usually means little, although we customarily start treatment with the vaccine which has given the positive reaction. If this fails to benefit we have no hesitancy in changing to another autogenous vaccine that has reacted negatively by skin test. Sometimes one, sometimes the other gives better results. Occasionally a stock vaccine works better than autogenous. Sometimes an autogenous mixed vaccine works better than an autogenous pure culture vaccine and vice versa.

A few patients derive definite benefit from vaccines. That it is not psychic is indicated by the fact that when one batch of vaccine is used up and a new one is made from fresh autogenous material, the patient may complain that the new batch is entirely devoid of effect. As far as the patient has known, this was the same vaccine. Then it becomes a real task to make a large number of autogenous pure culture vaccines in an effort to recapture the organism which appeared originally to be so beneficial.

Cooke has little use for nonspecific treatment of asthma in children. He dismisses as of no value tuberculin, typhoid vaccine, milk, calcium, peptone and polypeptids, given enterally or parenterally. He thinks somewhat better of vaccine for nonspecific immunity but prefers autogenous cultures. The production of hyperpyrexia with heat or intravenous vaccine appears to produce some effect but it is temporary and hardly worth the danger of exhaustion incident to these procedures.

Wilmer and Cobe doubt the specificity of bacterial vaccines as used today. Nevertheless they feel that the most logical procedure in vaccine therapy is that in which selected vaccines based on skin reactions are used in preference. They find that such vaccines give best results. They believe that mixed vaccines isolated from foci of infection have little to recommend them over stock vaccines. They believe that vaccine action, with vaccines used as they are today, is nonspecific.

Bray believes with Rowe and Piness that bacterial allergy plays little part in the allergic reactions of children. He feels that vaccines have not proved of permanent therapeutic value because: symptoms frequently return when vaccination is terminated; if treatment is continued and the dose increased, each inoculation appears to have a sensitizing effect, provoking an attack; while if the dose is not increased the vaccine does not appear to have any therapeutic effect at all.

Rackemann believes that for the most part vaccine treatment is non-specific, and feels that best results are obtained when injections are followed by local subcutaneous reaction of the delayed type.

Enteropathogens. Benson has studied the allergenic possibilities of organisms obtained from the intestinal tract. His report deals with methods and skin reactions, with little concerning results of treatment. However, he feels that benefit has been obtained in certain instances.

His method of isolation consists in the inoculation of a loopful of feces, preferably the last portion passed, into 5 cc. of sterile 1 per cent sodium carbonate. It is incubated in this overnight and plated on dextrose blood infusion agar plates. The first pour plate contains 0.5 cc. of the carbonate suspension. The second plate represents a 1:10 dilution of the first and the third a 1:100 dilution. Pathogens most frequently obtained by this method

are *Streptococcus viridans*, *hemolyticus*, *nonhemolyticus*, *Pneumococcus*, *Staphylococcus aureus*.

Testing is done intracutaneously with 0.02 cc. of vaccine. The reactions are read at the end of 15 to 30 minutes and after 18 to 36 hours. Immediate reactions are sometimes seen, but the delayed reaction is the more common type. Occasionally Benson found an organism of high antigenic titer which could be used as a stock organism. This was particularly true of *Streptococcus viridans*, with which he found that he sometimes obtained better results when treating patients allergic to *Streptococcus viridans* than with the *Streptococcus viridans* isolated from the patient himself.

He found that vaccines killed by heat at 60 degrees were usually more antigenic than those killed at 100 degrees. Sterile filtrates were of no value. Disruption of the bacterial cells by thorough grinding was of no benefit. Intravenous inoculation in certain cases produced better results than subcutaneous.

He found that patients usually gave positive reactions to the normal bacterial flora, as *B. coli*, *B. acidi lactici*, *B. aerogenes*, etc. This was to be anticipated since the normal body is immune to these organisms and would respond to local testing with a positive immunity reaction. Cohen has attempted desensitization with vaccines of this type, such as *B. coli*, and reports little or no evidence of benefit. With the pathogens mentioned above Benson finds no difference in antigenic activity between rough and smooth strains. He found that sodium ricinoleate tended to diminish antigenic activity.

He reports one interesting experience in local desensitization or local protection. It has been observed that a positive skin reaction appears to specifically desensitize the inoculated area sooner than the body as a whole. Applying this knowledge in the treatment of a case of pruritus ani, in which culture of the skin about the anus had yielded *Streptococcus viridans* and *Staphylococcus aureus*, he gave daily subcutaneous injections of a combined bacterial suspension of these organisms in scattered points about the anus. The pruritus which had been distressing and had persisted for a long time was promptly relieved after a few days of such injections.

Author's program.—I would emphasize the following principles which I have found quite reliable in vaccine therapy of asthma:

1. In approximately 1 per cent a small initial dose of vaccine causes exacerbation of symptoms. If the vaccine is still further diluted, a proportion of these patients report amelioration. This would suggest specificity in spite of the fact that there is no close correlation in my experience between this type of response and the presence or absence of either wheal or tuberculin type reaction. With better methods of vaccine preparation a correlation might appear.

2. A small initial dose may be followed by relief which can be prolonged by continued administration of the same dose. In such cases rapid increase in dose may cause return of symptoms, which are again relieved following return to the smaller dose. The parallelism between this and coseasonal pollen therapy is evident. This again suggests the possibility of specificity, which, however, cannot be correlated with the character of the skin reaction.

3. There are three possible types of response to vaccine treatment. With a given dose the patient may (a) improve, (b) become worse or (c) experience no change in his symptoms. If, following the preliminary injection, he reports improvement, the presumption is that the dose is proper for that patient and

should be held constant, without increase as long as he remains improved. If he becomes worse following his first injection, the presumption is that the dose was too large. The vaccine is therefore diluted ten or one hundred times and subsequent injections are given with this more diluted vaccine. If neither improvement nor exacerbation is noted, the presumption is that either the vaccine is not specific or the dose is too small. On the latter assumption the dose is successively increased until the patient reacts either with improvement or exacerbation. When improvement is at last achieved, the dose is kept steady.

4. Let us assume that the vaccine is nonspecific. The first injection was without effect and successive doses are gradually increased. Often a dose will be reached at which there is a delayed positive subcutaneous reaction of the pseudo-inflammatory type. At this point, improvement sometimes occurs, due to nonspecific factors, as described by Rackemann.

5. When one desires to obtain nonspecific bacterial effect of this type it can often be achieved more rapidly with gram-negative bacilli, especially colon bacillus and *B. prodigiosus*, which in my experience are especially likely to give delayed type of reaction. This appears to be nonspecific since it is observed in such a large proportion of cases. However, one is scarcely justified in assuming its nonspecificity since it may be but an expression of the specific natural immunity of the host to these particular bacteria.

The writer employs the above principles in other allergic manifestations presumably due to bacterial allergy, and in atrophic arthritis.

Discussion

Although the first concept of allergy was based on the reaction of tuberculin in the tuberculous person and allergy to bacteria has abundant bacteriologic basis, there is division of opinion not only as to whether therapy with bacterial vaccines is specific or nonspecific therapy, but as to whether there is such an entity as clinical asthma of bacterial origin. As Tuft (1945) points out, the symptoms usually cited as denoting bacterial asthma are the symptoms of infection. The diagnosis of bacterial allergy is made because other factors cannot be implicated and that there is no way by which a diagnosis of bacterial allergy may be proved. He insists that asthma with infection does not mean that the asthma results from the infection. It is probably true that those who have had the most experience with skin reactions to bacteria are least prone to depend on them as proof of etiologic relationship. A positive skin reaction may mean only that the patient was sensitized by some infection which may have come and gone in months or years past. It may indicate a skin sensitiveness but have no relationship to the present allergic reaction. Much more fundamental and painstaking investigation is needed to settle this disputed question.

CHAPTER LVII

FOCAL INFECTION

The Burky phenomenon has been discussed in the preceding chapter. If it should develop that a toxin secreted in a focus of infection can act as a hapten, it is conceivable that much of what we consider today as nonspecific focal infection may later be shown to be specific. For the present, however, this must be considered suppositional and in the following discussion we shall consider focal infection as a nonspecific incitant. While infection of this nature may play a part in all allergic manifestations, its greater importance is in the field of respiratory allergy.

Knott believes that bacteria in the bronchi form a histamin-like substance which nonspecifically stimulates smooth muscle spasm in otherwise predisposed individuals. He finds gram negative bacilli in the sputum the chief offenders. This needs further study.

Sinus Pathology in Inhalant Allergy

The relationship of sinus disease and nasal pathology to bronchial asthma still awaits solution. Some have claimed that asthma and vasomotor rhinitis are the result of nasal pathology and should be treated as such. Others insist that allergy is the only basis to be considered. Protagonists of both theories have amassed statistics, but we find these figures worthless for comparative analysis since they entail a variation out of all proportion to the number of cases studied. The incidence of sinus disease and gross nasal pathology in asthmatics has been reported as low as 14 per cent and as high as 90 per cent, with other figures ranging between. The incidence of sinus disease in asthmatic children has been reported as low as 6 per cent and as high as 100 per cent.

TABLE L.—PERCENTAGE OF ASTHMATICS SHOWING SINUS DISEASE OR GROSS NASAL PATHOLOGY (REVIEW OF LITERATURE)

AUTHOR	DATE	NUMBER OF CASES	FINDINGS	PATHOLOGY PER CENT
Francis	1929	402	N.P.	14
Gottlieb	1925	117	S.D.	26
Lublinksi		500	N.P.	29
Gill Cary	1930	110	S.D.	50
Adam	1900	640	N.P.	60
Dundas Grant	1913	107	N.P.	63
Tobey	1929	1000	N.P.	65
Schenck & Kern	1929	18	N.P.	67
Vaughan	1932	154	N.P.	71
Hansel	1925	400	S.D.*	75
Kern & Donnelly	1932	200	S.D.†	80
Smith	1929	‡	S.D.	82
Matthews	1914	300	U.R.L.	90

*Iridol positive; †X-ray studies positive; ‡Not stated.

S.D.—Sinus disease; N.P.—Gross nasal pathology; U.R.L.—Lesions of upper respiratory tract.

TABLE LI.—SINUSITIS IN ASTHMATIC CHILDREN

AUTHOR	DATE	NO. CASES	FINDINGS	PER CENT
Bullen	1930	235	S.D.	6
Chobot	1930	100	S.D.	41
Lierle	1926	20	S.D.	100

The majority of observers state that the incidence of gross nasal pathology or sinus disease is high in asthmatics. I found 71.2 per cent with evidence of past or present nasal pathology. Kern and Donnelly found in a study of 50 nonallergic controls that 72 per cent suffered from sinus disease. This figure was almost as great as their own recorded incidence of sinus disease in bronchial asthma, of 80.5 per cent.

TABLE LII.—RESULTS OF RHINOLOGIC TREATMENT IN ASTHMA

AUTHOR	NO. CASES	"CURE"	GOOD	BOTH
Kahn	N.S.	0 %	0 %	0 %
Heatley & Crowe	62	1.5%	0 %	1.5 %
Rackemann	Review of Literature	5 %	10.20%	10.20%
Bray	Review of Literature	14 %	—	—
Stout	Polyps	11 %	—	—
	Sinuses	22 %	—	—
Leopold & Fetterolf	24	20 %	—	—
Tod	202	10 %	49 %	59 %
Lierle	21	10 %	81 %	91 %
Smith	N.S.	74 %	26 %	100 %

N.S.—Not stated.

TABLE LIII.—RESULTS OF ALLERGIC TREATMENT IN ASTHMA

AUTHOR	NO. CASES	"CURE"	GOOD	BOTH
Walzer	Review of Literature	20-30 %	25-35 %	45-65%
Rackemann	425 Extrinsic	25 %	57 %	82%
	499 Intrinsic	18 %	52 %	70%
Vaughan	99 Extrinsic			68%
	55 Intrinsic			27%
Clarke		20 %	41.7%	61%
Menaugh	300	28.3%	27.7%	56%
Rowe	110	68.3%	22.7%	91%
Alexander and Zeek	69 Uncomplicated			90%
	123 Complicated			24%

When we study the results of treatment, we again observe figures that can scarcely be reconciled. The reported cures of asthma following rhinologic surgery range from zero to 54 per cent, while reports of satisfactory relief including cure and near cure range from zero to 100 per cent. Those who treat asthma as an allergic condition report cures in from 20 to 68 per cent and good results in from 24 to 91 per cent.

Obviously therefore figures are available to substantiate whatever stand one may choose to take. These series of results are not susceptible to direct comparison for several reasons. As a rule there has been no attempt to classify the patients, the feeling evidently being that the diagnosis of asthma was sufficient classification. But there are various forms of asthma, the two great groups being the extrinsic and the intrinsic; there are many types of exciting causes; and there are many kinds of contributory local pathology which play a part in the prognosis. Conclusions have usually been drawn

from studies of groups too small to warrant generalization. Too often only one aspect of the disease, either the rhinologic or the allergic, was considered. Surgical methods have varied widely. Finally, one suspects that the follow-up of end-results was frequently not carried over a sufficiently long period. Those who have had any wide experience with asthma know that, provided enough time elapses, a gradually increasing number of patients will again manifest symptoms.

Collaborative studies.—We may anticipate much more of value from the more recent method of investigation in which both the allergist and the rhinologist collaborate, realizing that allergic factors and nonallergic factors may interact in the production of symptoms. The progressive allergist today does not hesitate to call upon the otolaryngologist whenever indications arise, and increasing numbers of nose and throat men are recognizing an allergic intranasal picture in the presence of which they call upon the services of the allergist.

Any compilation of results that does not classify the asthmatic as extrinsic or intrinsic, or by some equivalent nomenclature, is inconclusive. The extrinsic case is a typically allergic asthmatic. The exciting cause is contact with some specific allergen to which the individual is sensitized and with which he comes into contact through the skin or the respiratory or digestive tracts, and from some source outside the body. In the pure intrinsic case, no such external excitant is discovered. Intrinsic asthma is sometimes spoken of as infectious asthma, but infection is probably not the only factor at work in the intrinsic case. Rackemann found 46 per cent of his asthma series intrinsic, Harkavy and Maisel found 47 per cent of theirs non-sensitive, and we have found 36 per cent to be intrinsic, Table LIV.

In hay fever, provided desensitization therapy is properly applied, results from allergic methods far excel those from any other form of treatment. No other method will ensure better than 75 per cent relief to over 80 per cent of patients and 90 to 100 per cent relief to two-thirds. Kern and Donnelly have shown that local nasal pathology, even actual sinus infection does not interfere with good results in hay fever. Hay fever patients with untreated sinus pathology did as well as those without sinus involvement.

Allergic therapy produces best results in extrinsic asthma and should be the method of choice. As in hay fever, good results are often obtained irrespective of local nasal pathology. Satisfactory relief in my experience was obtained in 68 per cent. This is about the usual conclusion; although Rackemann in a series of over 425 extrinsics reports better results, 82 per cent, while Alexander and Zeek report 90 per cent satisfactory relief in their uncomplicated cases. The results with intrinsics following allergic therapy are quite different. While Rackemann reports 70 per cent with adequate relief, most figures are lower, my own being 27 per cent and Alexander's, 24 per cent.

There is the residual group of extrinsics, probably about 25 per cent, and the entire group of intrinsics, in whom relief may sometimes be secured through rhinologic treatment. This gives us roughly about half of the chronic asthmatics in whom nasal or other local nonspecific pathology may require adjustment.

Survey of rhinologic factors. The following survey of the rhinologic factors is based on a series of 154 asthmatics selected out of a total series of

300. The only requirements in the selection were, adequate available information from rhinologic study along with the allergic study, and adequate follow-up over a period sufficiently long to determine results.

TABLE LIV.—DISTRIBUTION OF 154 ASTHMA CASES WITH RESULTS OF TREATMENT

RESULTS	EXTRINSIC 99 CASES (64%)	INTRINSIC 55 CASES (36%)
Excellent	38.4%	10.9%
Good	29.3	16.4
Fair	15.1	10.9
Poor	15.1	52.7
Bad	2.1	9.1
Good and excellent	67.7%	27.3%
Fair, good, and excellent	82.8%	38.2%

Of the total series 36 per cent were intrinsic asthmatics and 64 per cent were extrinsic. Results were classified as excellent, good, fair, poor and bad. The bad result cases included those who for one reason or another became worse during their period of supervision. Including the excellent and good cases, 27.3 per cent of the intrinsics and 67.7 per cent of the extrinsics obtained adequate relief from allergic methods only. If we were also to include the fair result cases, these figures would be 38.2 per cent for intrinsics and 82.8 per cent for extrinsics. These figures approach more nearly those reported by Rackemann, but in order to avoid too optimistic a tendency, in the remainder of this discussion we shall consider only the first two classes as having obtained satisfactory results.

Of the entire series 33.8 per cent had previously been subjected without relief to nasal surgery. Thirty-two of the 47 were extrinsic cases, cases which should not have been treated surgically without preliminary allergic study.

TABLE LV.—ANTECEDENT NASAL SURGERY IN 139 CASES

Extrinsic (95 cases)	32 cases
Intrinsic (44 cases)	15 cases
Total	47 cases or 33.8%

Of 95 extrinsics 32 had been subjected to nasal surgery. Of these 32, 15, or 47.9 per cent, reported good results from allergic therapy. Sixty-three had had no precedent nasal surgery, and of these, 47, or 74.6 per cent, reported good results from allergic treatment. In the extrinsic group the results were much better among those who had not had previous nasal surgery. One might argue that the poorer results in the operative cases were due to the presence of local nasal pathology, or one could argue equally well that the fig-

TABLE LVI.—EFFECT OF NASAL SURGERY ON RESULTS OF ALLERGIC TREATMENT

	EXTRINSIC	INTRINSIC
No. cases	95	44
No. who had had surgery	32	15
No. of latter with good results	15	2
Per cent with good results	47.9	13.3
No. who had not had surgery	63	29
No. of latter with good results	47	11
Per cent with good results	74.6	38.0

ures indicate that in extrinsic allergy nasal pathology is better left alone, certainly until allergic therapy has been given a trial. In favor of the latter is the observation that 27 or nearly three-fifths of those who had had no surgery and reported good results, did actually have nasal pathology, and the good results were obtained in spite of the fact that this was not treated.

I believe that there is some truth in both arguments, since the same differences were observed in the intrinsic cases. Of 44 intrinsic cases 15 had had antecedent nasal surgery, and of these only 13.3 per cent reported good results. Of the 29 who had not been subjected to surgical treatment, 38 per cent reported good results.

One conclusion, however, stands out definitely, that relief can often be obtained by allergic methods alone, even in the presence of nasal pathology. At the same time nasal pathology is often a deterrent to adequate relief both in the intrinsics and in some of the extrinsics. Taking both groups together, 40 showed evidence on physical examination of nasal pathology and had had previous nasal surgery. Of these only 35 per cent reported good results.

TABLE LVII.—NASAL PATHOLOGY AS A FACTOR IN RECOVERY—132 CASES

	NO. CASES	PER CENT OF GROUP	NO. RELIEVED ALLERGICALLY	GOOD RESULTS PER CENT
1. Nasal pathology treated	40	30.3	14	35.0
2. Nasal pathology not treated	54	40.9	32	59.3
3. No nasal pathology	38	28.8	26	68.4
4. Nasal pathology (1 and 2)	94	71.2		
5. 1 and 2 subjected to previous surgery			42.5%	
6. Showing nasal pathology but not operated on			58.7%	

Fifty-four had not had previous surgery but did show evidence of nasal pathology on physical examination, and of these, 59.3 per cent reported good results. But best results were obtained in the 38 who showed no evidence of nasal pathology and gave no history of nasal treatment and who reported 68.4 per cent with satisfactory results. These 38 are obviously strictly allergic cases and could expect no relief from any form of nasal treatment. They represent 28.8 per cent of the entire series.

Summarizing this portion of our discussion, 71.2 per cent of the series showed evidence of gross nasal pathology either in the past or at the time of first examination. Of those showing nasal pathology, 42.5 per cent had been subjected to some form of surgery. Results were decidedly better among those who had had no previous surgery, even though 59 per cent of these had clinical nasal pathology, which was not treated. The ethmoid region has long been considered an asthmogenic area in certain cases, and we find evidence that, other factors not considered, patients with turbinate pathology do not do so well as those without.

The inference is that from the rhinologist's point of view the early treatment of an asthmatic with local nasal pathology should be conservative, non-surgical. If these measures do not achieve adequate relief, a complete allergic study should then be made and allergic therapy should be carried out long enough to obtain as good results as may be obtained by this method. Following this, if relief is still inadequate, more radical nasal surgery may be undertaken as indicated. There is no gainsaying that sinus surgery occasionally produces spectacularly good results in asthma. Unfortunately it is usually not permanent.

For example, Schenck and Kern observed that following the Caldwell-Luc operation 83 per cent experienced complete relief. In one-third of these the relief continued for from three to seven and one-half months. In slightly over half, the relief was temporary, lasting from a few weeks to two years; 17 per cent had no relief at all. Even this operation does not necessarily permanently cure the antrum infection. They found in patients who had had previous Caldwell-Luc operations that the antra contained dense, fibrous tissue with loculated collections of pus and polypoid tissue.

Therapeutic program. It becomes apparent from the preceding discussion that the attitude of the allergist toward local nasal therapy is one of conservatism. Obstructing polyps should be removed particularly if there is not a speedy response to allergic therapy. Submucous resection is not indicated unless for the relief of contact and definite obstruction. Turbinatectomy is to be avoided since following this operation cooler rawer air enters the bronchial tree and this sometimes produces exacerbations of the asthma. Since asthma is sometimes relieved by allergic methods in spite of local nasal pathology, these should be tried first. On the other hand, if in spite of adequate trial with allergic therapy and conservative nasal therapy the condition persists, and if there is evidence of sinus pathology, more radical procedures should be inaugurated. In such cases the operation of choice should be that which offers greatest promise of relieving the sinus condition, quite irrespective of the presence or absence of an allergic state. Nasal surgery will be indicated more often in the intrinsic type of asthma than in the extrinsic. This represents 35 to 45 per cent of chronic asthmatics.

What we have said concerning chronic asthma applies equally to chronic vasomotor rhinitis. In both conditions best results will be obtained from close cooperation between the rhinologist and the allergist. Even so, we shall find that there is a certain residual percentage which will not respond even to these combined efforts and which impresses upon us a realization that, in spite of all of the advances in our understanding of the allergic diseases, we are still in large measure ignorant of the underlying pathologic process which makes one person appear allergic and another nonallergic.

Further discussion of sinus surgery appears in Chapters LXXII and LXXIII.

PART IX

FUNGI

The weeds of the culture room

—CHARLES THOM.

CHAPTER LVIII

CHARACTERISTICS AND IDENTIFICATION OF YEASTS AND MOLDS

The allergist finds that he must become conversant in many fields outside of medicine. In addition to being a reasonably good field botanist he must either become a laboratory mycologist or secure the aid of one. Since the majority have not been faced with the problem of the classification and identification of air-borne fungi which may be allergenic, the following pages contain a brief synopsis of those phases of mycology with which the allergist must acquaint himself.

Molds and Yeasts

In the development of the plant kingdom, molds appear slightly above the bacteria. There is evidence that they were first aquatic, derived in part at least by a retrograde evolutionary step from algae, from which the chlorophyl had become lost.

Distribution and habitat. Molds are found in most localities. They need little nourishment provided moisture is sufficient. During prolonged rainy weather they will grow on the backs of books and on canvas, obtaining sufficient nourishment from the organic matter therein contained. They are usually present in the ground to a depth of at least four feet although they are most numerous in the first six inches. Unlike bacteria they prefer an acid substrate, growing in a medium the acidity of which prevents the growth of bacteria. Special laboratory media are therefore prepared of relatively high acidity, in which molds grow in abundance, but bacteria, little or not at all. Two hundred and sixty-five species of molds have been isolated from the soil. In one fertilized soil with pH 4 acidity 129,000 fungi were found per gram of soil.

Function.—Molds in the soil serve a utilitarian purpose. Since they possess no chlorophyl they cannot synthesize starches and must depend upon previously synthesized material, becoming thereby obligate parasites or saprophytes. In the ground, they decompose complex organic substances, breaking them into their simpler constituents thus providing nutrition for plants. They are chiefly responsible for the decomposition in the ground of cellulose and wood. They assimilate soluble inorganic nitrogen compounds and minerals, thus fixing them in the soil as fertilizer, preventing their leaching out in the water.

There is a symbiotic relationship between molds and the roots of certain plants. They take the place of the root hairs, completely surrounding roots

and in some cases even penetrating them. They decompose the organic matter surrounding the roots, thus rendering it available for the plant itself. The orchid cannot exist without its symbiotic mold.

Atmospheric molds. Molds or more particularly their spores occur in the air, with some seasonal variation, being most common in the summer months. They are present in the dust of houses, especially damp houses. Being in the air and deposited on various articles we can understand from our knowledge of their growth requirements why they play a part in the spoilage of certain foods, such as fruits, jellies, preserves, acid fruit juices, syrups, ham and other meats, bread, butter and sour milk and cheese. They grow in pickling vats and, when enough moisture is present, on leather, linen and cotton, forming mildew. Outdoor air often contains from 100 to 4,000 bacteria and molds per cubic meter. On a windy day the count may be higher. Counts indoors have been made as high as 250,000 per cubic meter.

Economic status.—Molds have a certain economic importance.

1. They are important in the spoilage of foodstuffs.
2. In the spoilage of other products of industry.
3. As stated above they are important in the circulation of organic material, in producing fertilizer in the soil.
4. They produce disease in plants, animals and man.
5. Their enzymic activity has been utilized in certain industries.

In the Orient a mold is used to convert rice into sugar for the manufacture of alcoholic beverages. There and in this country *Aspergillus oryzae* (aspergillus of rice) is employed for the manufacture of a diastatic ferment, marketed as Takadiastase, so called after its inventor, Takamine. The citromyces and other molds have been used for the manufacture of citric acid. The dark brown sauce used in Chinese restaurants is a product of the fermentation of *Aspergillus oryzae*.

Many cheeses are ripened with molds, the most important of which are Camembert and Roquefort which are ripened through the activity of the proteolytic ferments of a penicillum. Yeasts are employed in the fermentation of wines and beers and the making of bread.

Characteristics.—Fungi or molds grow in irregular masses usually made up of densely or loosely woven strands or filaments termed *mycelium*. Such a mass is a *thallus*, a simple plant body not differentiated into root, stem and leaf. The fungi or *thallophytes* are thallus plants. Algae, aquatic chlorophyll-containing plants, belong to the same group. The latter by virtue of their chlorophyll content can synthesize their own food, the former must have organic matter for growth.

There is a third group of thallophytes (the lichens), composed of algae and fungi growing in symbiosis.

Classification.—There are three general groups.

- a) Eumyces (true molds).
- b) Schizomyces (fission molds or bacteria).
- c) Myxomyces (slime molds).
- d) There is another group, actinomyces, pathogenic for man, which is probably intermediate between a) and b). The eumyces are divided into two groups: (a) molds (unicellular or multicellular), (b) yeasts (always unicellular).

Mycelium, hyphae.—Molds may be unicellular or multicellular. Yeasts are always unicellular, although they may be temporarily attached in clusters

or chains. As to whether true molds exist as unicellular or multicellular forms depends in great part upon their environment; in certain cultures they tend to be unicellular, in others multicellular. They have as their characteristic tissue, *mycelium*, consisting of threads of cells attached end to end, forming long filaments, usually branched and interwoven until they make the bulk of the mold

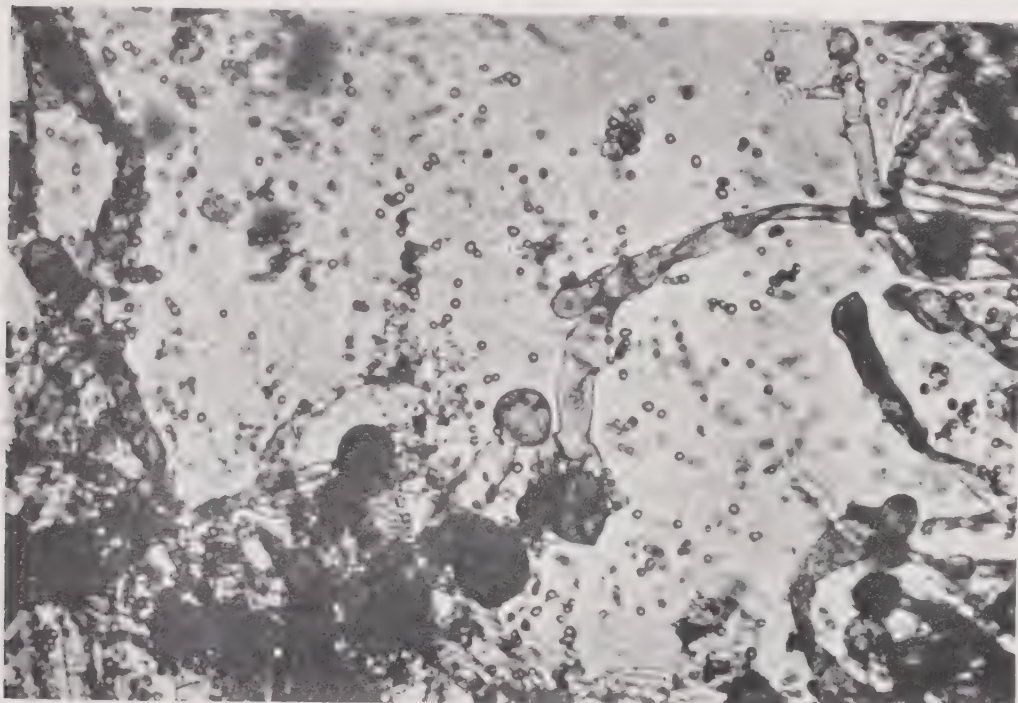


Fig. 224.—*Mucor*. Showing minute spores and nonseptate mycelium.



Fig. 225.—*Monilia*. Showing septate mycelium and budding.

as we see it. In some the mycelium is loosely meshed, resembling cotton wool. In others it is closely meshed like a pad of velvet. Classification in accordance with the characteristics of the mycelium is unsatisfactory because the mycelia possess no special characteristics differentiating one from another, although there is one large group with a characteristic mycelium. In this particular case a

study of the mycelial hyphae is of value in classification. In many molds the *hyphae*, the individual threads of the mycelium, show partitions separating the cells from one another. In this case we speak of the mycelium as being *septate*. There is a large group in which the mycelium is *nonseptate*, with no partition between the individual cells.

When mycelium is septate each constituent cell has its nucleus or nuclei. When it is nonseptate the nuclei are scattered through the protoplasm.

Diagnostic characteristics of mycelium.—In the study of molds the first question to settle microscopically is whether the mycelium is septate or not. If it is not, the mold probably belongs to the great group, phycomycetes or alga-like fungi. There is one exception, in that fungi with septate mycelium sometimes fail to show septa early in the period of rapid growth although septa are developed as they mature. It is the phycomycetes (“seaweed fungi”) especially which are presumed to have been derived by a retrograde evolutionary process from the algae.

The phycomycetes, of which *mucor* is an example, usually develop loose mycelium presenting a cotton wool appearance. The ascomycetes on the contrary present a more velvety appearance. The denseness of the mat is to a great extent a determinant of the physical appearance. It may be so dense as to actually present a fleshy appearance, as in the mushroom.

Bases of mold classification. The next two outstanding groups in which we are interested after the phycomycetes are the ascomycetes and the fungi imperfecti. An understanding of the basis for the classification into these two latter groups is essential to proper differentiation.*

As with foods and the higher orders of plants, so with the molds; two species may resemble each other very closely and yet belong in entirely different groups while two closely allied fungi may present few points of resemblance.

In all botanical classifications it has been found safest to classify families, genera and species according to their evolutionary and genetic relationships, in other words according to the characteristics of their reproductive tissues.

Reproduction.—Certain fungi reproduce asexually as do bacteria, by the dividing of one cell to become two cells. Others reproduce sexually, by the union of two cells, male and female, or positive and negative. The single cell resulting then divides to produce several. Sexual cell union in the ascomycetes results in the production of a seed-like organ containing several spores, usually 8. This organ (termed an ascus) usually develops in the mycelium and is a resting stage from which new molds are later developed in an appropriate environment. The presence or absence of asci is a criterion as to whether the mold belongs to the large family of the ascomycetes. Any simple mold which forms asci belongs in the *ascomycetes*. That is, a sexual cycle has been demonstrated. There are molds in which no sexual cycle has ever been demonstrated and these are appropriately termed imperfect fungi or *fungi imperfecti*. Many which have been classed as fungi imperfecti have since been found under certain conditions to produce asci and ascospores. As

*There is an additional group of molds organically more complex, the basidiomycetes, the large fleshy fungi such as mushrooms, puff balls and bracket fungi.

Eumycetes

1. Phycomycetes
2. Ascomycetes
3. Basidiomycetes
4. Fungi imperfecti

For present purposes we are not interested in the basidiomycetes.

soon as this is demonstrated such a fungus is taken out of the class fungi imperfecti and placed in the class of ascomycetes. So, it will be seen that the fungi imperfecti are in a measure a heterogeneous group in which no sexual reproductive process has been demonstrated but in which we should bear in mind that it may be demonstrated at some future time.

Classification based on characteristics of sexual reproductive tissues.—Unfortunately for easy classification of molds, asci are rarely seen when they are grown in the usual laboratory media. The substrate is the important element in determining the development of asci. If a mycologist wishes absolutely to identify a mold in the accepted classifications such as that of Saccardo, he must grow that mold in a variety of special culture media until he has been able to demonstrate sexual reproductive tissues. So, as far as the routine study of molds in allergy is concerned we are faced with the problem of classification based upon organs which we rarely see in our work. Fortunately there are other characteristics which enable identification. The logic of the classification, however, in accordance with these secondary characteristics disappears unless we realize that the basis is the manner of reproduction. For example, there is an aspergillus in the ascomycetes and there is another aspergillus almost indistinguishable from it, away off from it in the Saccardo classification, in the fungi imperfecti. The difference is that in one of the aspergilli asci have been produced while in the other they have not been found up to the present.

So, in studying texts on mycology we will observe two types of classifications. The standard is that of Saccardo which has been very ably condensed with slight modification by Stevens, but on studying Stevens for the identification of any particular mold we at once reach an *impasse* since the discussion throughout his text has to do with the presence or absence and characteristics of asci and ascospores.

Classification based on secondary reproductive characteristics.—For practical purposes we must use classifications based on secondary characteristics and in this classification one of the most useful is that used by Buchanan. I would again emphasize that his classification appears confusing until one realizes that the general principles are based on the presence of a phenomenon which we do not actually see and identify in the mold. In short our problem becomes not so much one of classification as of identification. The situation is somewhat analogous again to the situation with foods. We know there is a genetic classification but we are more interested for epicurean purposes in their classification into green vegetables, starchy vegetables, fruits, nuts, etc.

What are these secondary determining characteristics on which identification is based?

Mycelium.—

1. Nonseptate—phycomycetes.
2. Septate—one nucleus per cell—ascomycetes.
3. Septate—two nuclei per cell—basidiomycetes.

Normally fungi reproduce from spores which germinate, forming mycelium. At first nonseptate, this becomes septate except in the phycomycetes. As the mycelium continues to grow, it may divide into two types: (a) vegetative portion, (b) reproductive portion. The vegetative portion varies little from one mold to another but the reproductive portion differs a great deal in different molds, thereby facilitating differentiation. Occasionally there is a third type,

(c) mycelia sterilia, in which no reproductive organs are formed. It is obvious that in this particular mold only the vegetative mycelium is present and such a mold therefore cannot be identified. The development of mycelia sterilia usually depends on nutritional conditions in the media.

Oidia.—In addition to spores many species reproduce by the formation of yeast-like cells, or oidia. These may separate off from any part of the mycelium, either at the end, or as lateral buds. When they have separated they may continue to reproduce by budding, giving the appearance of yeasts. In the proper media they will return to mycelium formation. Oidia may form in any of a large variety of molds. They are not peculiar to any single class. The absence or presence of oidia is therefore usually not of value in classification or differentiation although some fungi develop oidia so regularly and so constantly in contrast to others that this phenomenon is sometimes of help in identification. An example is *Oidium lactis*.

Oidia form as the result of segmentation of mycelium which constricts and splits off. Once formed they may produce new cells by budding, which in turn may again produce mycelium.

Oidia are not spores. They are vegetative forms which are not more resistant to lethal factors than the mycelial cells themselves. They are growth forms rather than resting forms. The conditions of growth determine their appearance. When they are present in preponderance the mold may be mistaken for yeast, especially if they continue to reproduce by budding.

It seems probable, as a matter of fact, that yeasts have developed by a retrograde process from the higher fungi as a result of having permanently lost the power to produce mycelium. True yeasts no longer produce mycelium but they do form spores.

The yeasts are rather a heterogenous group of fungi which permanently remain in unicellular form. They are not a unit class, but are grouped together for convenience.

Spores.—Spores are very constant in different fungi and possess recognizable characteristics of formation and grouping. They are reproductive bodies and are therefore useful in classification. They may be (a) sexual or (b) asexual. Some molds produce both sexual and asexual spores simultaneously. Others produce only sexual forms on one host and asexual on another host. This is characteristic of the rusts.

In some molds true spores are produced in the same way as oidia either by terminal budding or lateral budding. This reproduction is asexual.

Chlamydospores. Another form of asexual spore develops in the mycelium, with a thickened protective covering, in the center of which are the spores. These are the chlamydospores. They are observed occasionally on laboratory media but are of no great importance in differentiation. Like oidia, they are not peculiar to any one class of fungi and as a matter of fact they are especially frequent in species which produce oidia frequently. As a consequence one often finds both chlamydospores and oidia in the same fungus.

Zygospores.—Sexual reproduction is accomplished in two ways. The phycomycetes produce zygospores while the ascomycetes produce ascospores. In the former terminal hyphae of the nonseptate mycelium approach and attach themselves to each other, following which there develop constrictions near the point of fusion, forming two cells, suspended by the nonseptate mycelium. The nuclei of the two cells fuse and divide—the cells themselves

fuse. These enlarge and the spore forms in the interior. This is the zygospore. Under proper conditions the zygospore germinates, producing new mycelium with its asexual spores.

Ascospores.—The *ascospore* is characteristic of molds with septate mycelium. Two hyphal cells fuse and the nuclei reproduce. Neighboring hyphae proliferate to form a dense protective mat or wall, the peritheciium, around the spore. The central portion of this ascus develops into ascospores, varying in number, but usually eight.

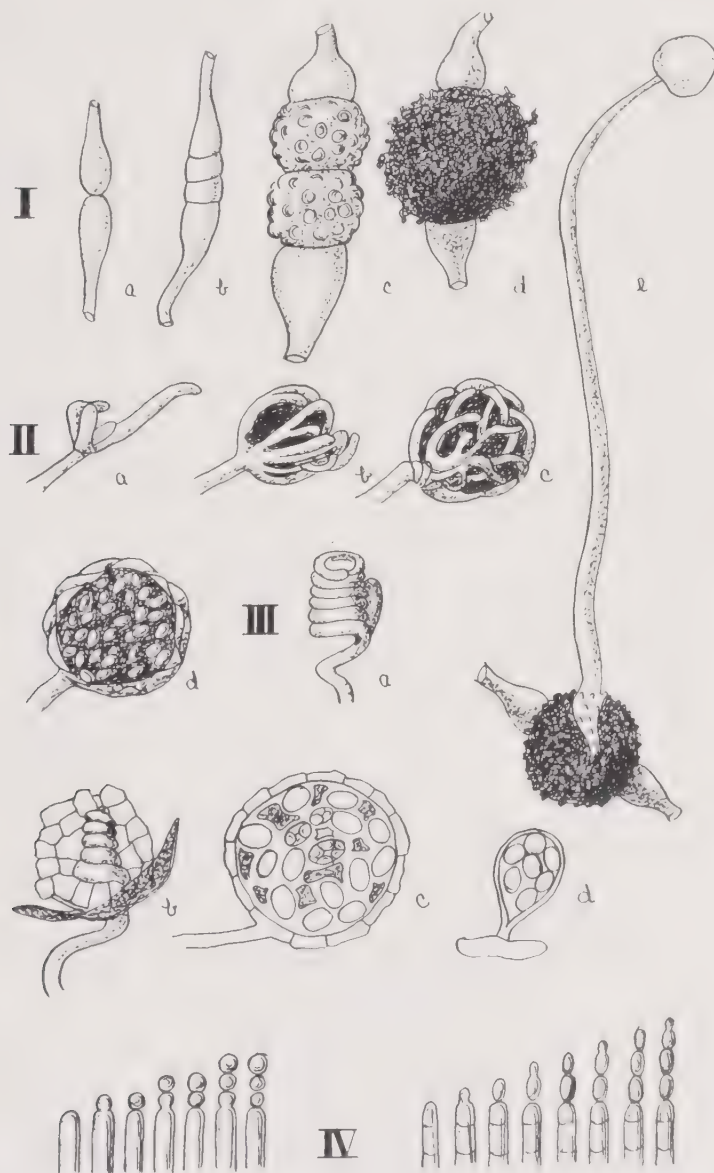


Fig. 226.—Sexual reproduction in fungi.

I. Formation of zygospores in *Mucor*. In *a*, two hyphae come into terminal contact; *b*, two gametes are formed at the point of contact; *c*, gametes fuse; *d*, the ripe zygospore remains supported by suspensors remaining from the original hyphae; *e*, the zygospore germinates, producing a sporangium stem. (After Henrici.)

II. Formation of ascospores and asci. Sex cells develop on hyphae *a*, and become surrounded by a peritheciium, from growth of sterile hyphae, *b* and *c*. Spores develop on the inside *d*. (After Buchanan.)

III. Development of the peritheciium from sterile hyphae *a* and *b*; *c* and *d*, mature ascus with ascospores on the interior. (After Buchanan.)

IV. Differentiation between the formation of conidia (spores), and vegetative budding. In the former the terminal spheres are larger, active reproduction being from the stem. In the latter, terminal spheres are smaller, representing budding cells. (After Buchanan.)

Sporangia and sporangiospores.—Asexual spore production is accomplished in the phycomycetes as a rule with the formation of the sporangium. Specialized reproductive hyphae develop from the vegetative hyphae. At the end there develops a terminal enlargement containing several nuclei which divide repeatedly with the result that a large spherical organ is formed containing many nuclei, with some supporting connective tissue. The nuclei migrate

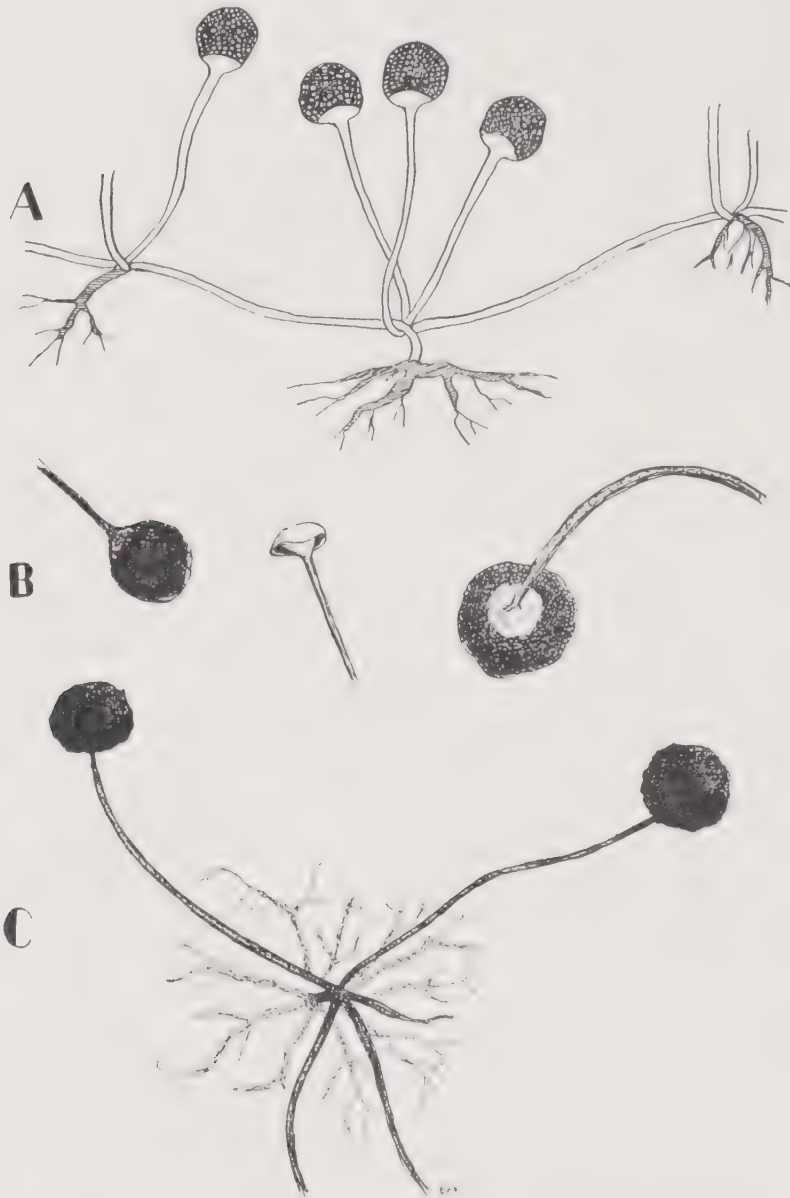


Fig. 227.—Phycomycetes. A, Showing nonseptate mycelium, sporangiophores, sporangia filled with spores, columella, stolons, and rhizoids. (*Rhizopus*, after Buchanan.) B, Views of sporangia and (center) columella after rupture of spore sacs. (After Buchanan.) C, Surface view of sporangia and sporangiospores, with rhizoids.

or are pushed toward the periphery. A cell wall develops around each nucleus, thus forming the spore. The membrane of the original terminal swelling becomes a thin membranous sac filled with spores. The central part of the sphere persists as a supporting tissue, the columella. When the spores are matured, the membrane ruptures, liberating them and leaving the stalk with the bare columella and often a small collar of the spore case at the base of the columella.

The entire spore sac is the sporangium. This type of spore is termed sporangio-spore. The reproductive hypha is the sporangiophore—the carrier of the sporangium.

Conidiophores and conidia.—The spores of the phycomycetes are usually enclosed in a spore case (sporangium). Those of the ascomycetes are usually free. They may develop merely as single spores or a chain of spores at the end of the reproductive hyphus in which case they resemble oidia. The spores of

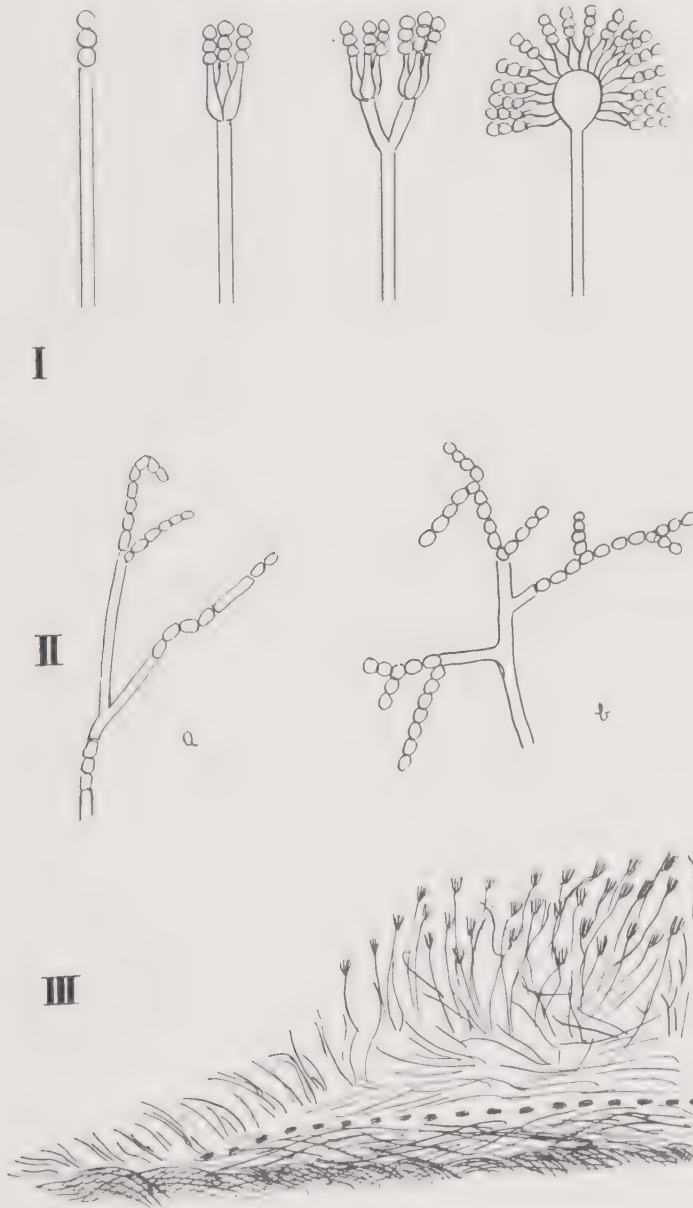


Fig. 228.—Fungi.

I. Gradations of complexity in different molds, from simple terminal conidia, as in monilia, through monoverticillate and biverticillate penicillia, to aspergillus. In the simplest, conidia are attached directly to the conidiophore. In penicillia, sterigmata separate the two. The general picture is of a brushlike mass. In aspergillus there is still further separation by a terminal inflation of the conidiophore (the vesicle).

II. Monilia. Conidia develop directly from mycelium. The proximal mycelium may be considered a conidiophore.

III. Only mature growing fungus develops conidiophores and sporangia. Colonies should therefore be fished from the center. The illustration shows absence of reproductive elements at the margin of a growing colony. Since diagnosis depends upon the spore picture and young colonies may fail to show this, they should be allowed to continue to grow until the former develop.

the ascomycetes are termed conidia. There are usually specialized cells termed sterigmata at the end of the hyphus from which the conidia develop. In certain molds several parallel sterigmata develop at the end of a single reproductive hyphus or conidiophore. Each sterigma produces and supports its own chain of conidia. Several sterigmata with their attached conidia grouped together on one conidiophore give the appearance of a small brush. The group of molds which produce this type of asexual reproductive organ is termed penicellium or "brush like" mold. Some molds develop terminal enlargements or globose ends to the conidiophore. Large numbers of sterigmata are produced around the circumference or surface of the globose ends. Those again support chains of conidia. The impression is that of a medusa-like cluster of chains. Molds producing this type of asexual spores are classed as aspergilli. In both aspergilli and penicillia the primary sterigmata may each produce two secondary sterigmata thereby doubling the chains of sterigmata. This is of importance in the differentiation of various species. The important differentiating point, however, between the penicillia and aspergilli is the presence or absence of the globose end "or vesicle" in the conidiophore.

Factors in identification.—The identification of molds depends upon

1. Gross appearance (density and color of the mat)
2. Whether hyphae are septate or not
3. Grouping and placement of conidia
4. Size of conidia
5. Shape and branching of conidiophore
6. The sterigmata (primary or primary and secondary)
7. Presence or absence of vesicle
8. Position and characteristics of sporangiophore
9. Size and shape of columella
10. The placement, arrangement and internal structure of the spores (conidia and sporangiospores)

Conidia may be

- Spherical
- Oval
- Cylindrical
- Fusiform
- Club shaped
- Irregular
- Star shaped
- Unicellular or multicellular

Among the aspergilli, for example, the characteristics requiring study for identification are

1. Size and form of the vesicle
2. Number and arrangement of the sterigmata
3. Presence or absence of secondary sterigmata
4. Size and form of conidia
5. Height of conidiophore
6. Color and position of perithecia around ascospore when present
7. The form of the ascospore when present
8. Color of the mycelium and of the conidia

The Phycomycetes

While there are thousands of varieties of molds, relatively few are found in the dust of houses, laboratories, etc. Among the phycomycetes, fungi with nonseptate mycelium, there are two genera which the allergist and bacteriologist see frequently. These are mucor and rhizopus in the genus *Mucoraceae*. Grossly, they appear very similar, resembling cotton wool, but are differentiated chiefly by the fact that rhizopus possesses aerial rhizoids or roots.

In Petri plates these roots or "holdfasts" become attached to the top of the plate. They can be easily seen especially as they are torn away on opening the dish. The cover should be inverted and studied under low power. The rhizoids or roots of rhizopus are connected by runners or stolons comparable to those observed in crab grass or in the strawberry. In rhizopus the sporangiophores arise directly opposite rhizoids. The following table serves to differentiate.

TABLE LVIII

	MUCOR	RHIZOPUS
Rhizoids	Absent	Present
Aerial Rhizoids	Absent	Present
Sporangiophores	Arise anywhere	Arise from nodes
Columella	Never hemispherical	Rests in a cup-shaped depression of the sporangiophore called apophysis
Spores	Always smooth and regular	Frequently angular and collapse readily in water

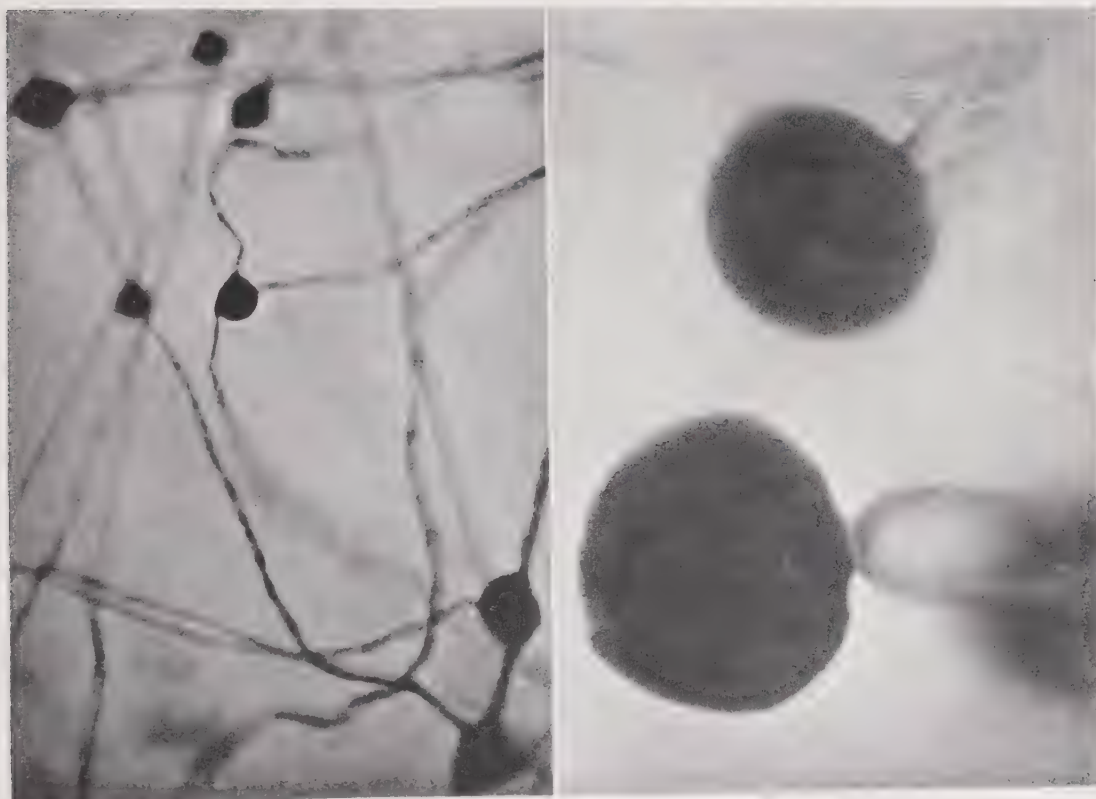


Fig. 229.—Mucor. Left figure shows sporangia and mycelium as observed through low-power microscope focused directly on Petri plates. Right figure shows high power of sporangia (spore sacs) and sporangiophores or stalks.

Mucor and rhizopus. There are over 50 species of mucor which are differentiated by study of:

1. Type of branching of the sporangiophore.
2. Form, length and thickness of columella.
3. Dimensions of spores.
4. Diffuence or fragility of the membrane.
5. Shape of spores.
6. Diameter of sporangium.

The most important of these six characteristics is the branching of the sporangiophore, best observed in slide culture. It is often difficult otherwise to study this branching because the hyphae and sporangiophores become twisted and difficult to distinguish. Young and immature sporangiophores are often unbranched. Therefore one should not examine for branching at the edge of a growing colony. There are three general types of branching useful in classification.

- (a) Monomucor (unbranched)
- (b) Racemomucor (main stem and lateral branches)
- (c) Cymomucor (irregular branching)

There appears to be one mucor which is pathogenic for man (*corymbifer*) which has been found in diseased lung tissue.

Rhizopus nigricans is the commonest of the phycomycetes. It is responsible for "leak" in strawberries, and soft rot in sweet potatoes. When it occurs as a contaminant in a bacteriologic laboratory it rapidly overgrows culture plates.

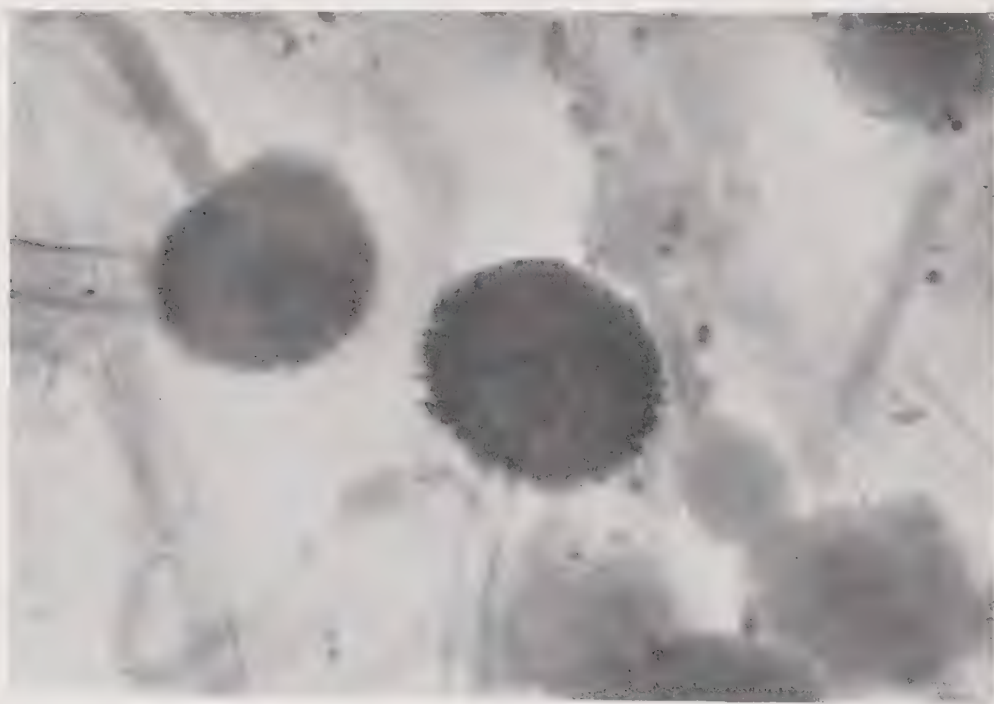


Fig. 230.—*Rhizopus*. Note resemblance to *mucor* and absence of septa in mycelium.

The Ascomycetes

Among the ascomycetes the class of chief importance in the present study is the hyphomycetales. There are two general families in this class, differentiated according to the color of the mycelium. If the mycelium is white or brightly colored the mold belongs in the class (a) *Mucedinaceae*. If it be dark or smoky, black, brown or olive the ascomycetes belongs among the (b) *Dematiaceae*. The color of the mycelium may differ entirely from that of the conidia and for this reason it is desirable to examine not only the top surface of the colony but also the reverse side of the Petri dish through the culture medium. While there are many genera and species of hyphomycetales the great majority are rare. Those of interest to the allergist and bacteriologist are found in a

very few genera. Indeed, three-fourths of the hyphomycetales observed in routine work are represented by *Aspergillus* and *penicillium*.

Aspergillus.—As mentioned above this group presents a characteristic arrangement of conidia and conidiophores. The latter are unbranched, arise from enlarged cells of the vegetative mycelium known as foot cells and terminate in a swollen vesicle. Attached to the vesicle are stalks of sterigmata



Fig. 231.—Varieties of aspergilli. There may be a single group of sterigmata to which conidia are attached (III) or there may be primary and secondary sterigmata (IV). These are not equatorially placed as in the diagram but cover the entire vesicle (I, II, V). *Citromyces* (V) is usually classed apart from *aspergillus*. (After Buchanan.)

somewhat resembling tenpins in appearance. The sterigmata may branch, giving rise to secondary sterigmata. Either the primary sterigmata or secondary sterigmata when present bear chains of conidia. The result is a compact mass or head at the tip of the hypha. *Aspergillus glaucus* and *Aspergillus nidulans* frequently form ascospores.

Various species of aspergilli are identified to a great extent by the color of the spores, but it should be borne in mind that the color depends upon the age of the colony. If too young or too old, the color is unreliable. While the color of the conidia varies, that of the mycelium as seen on the reverse side of the plate is usually reddish or brownish.

Characteristics to be studied microscopically, for identification, include the size and shape of the vesicle, of the sterigmata, of the conidia and the presence or absence of secondary sterigmata.

Thom and Church describe 66 valid species of aspergilli. *Aspergillus fumigatus* occasionally infects the lung of man, and more frequently the respiratory tract of birds.



Fig. 232.—*Aspergillus*, as seen in specimen teased in saline on slide.

Penicillium.—There are over 600 species described by Thom. Differentiation is not as easy as with the aspergilli. Indeed, they form such a large and intricate group that there are “penicillists” who devote much of their time to study of the penicillia. The outstanding characteristic of this group is that the conidia are produced from sterigmata which occur in whorls or clusters known as verticils, which take their origin from the tip of the conidiophore. The conidiophore presents no terminal enlargement or vesicle, as is seen in the aspergilli and there are no enlarged foot cells.

Formerly all green penicillia were termed *Penicillium glaucum* but since this is too indiscriminate the designative term *glaucum* should be avoided in the identification of penicillium. The former *Penicillium glaucum* has been subdivided into several species. Color is still of some value in identification, but the size and structure of the conidia and conidiophores, the gross appearance of the colony, biochemical reactions of the mold, and knowledge of the natural habitat or substrate are more important.

Thom divides penicillia into 4 general groups depending upon the manner of branching of the spore head, the spore head being that portion attached to the tip of the conidiophore.

1. Monoverticillata (a single whorl of sterigmata).
2. Biverticillata (forking sterigmata with secondary sterigmata forming symmetrical whorls).
3. Polyverticillata (further subdivision in symmetrical fashion producing a large number of whorls).
4. Asymmetrica (symmetrical distribution of sterigmata and whorls).

Group 4 contains the more important species. There is some variation in all four groups but the dominant tendency is apparent.

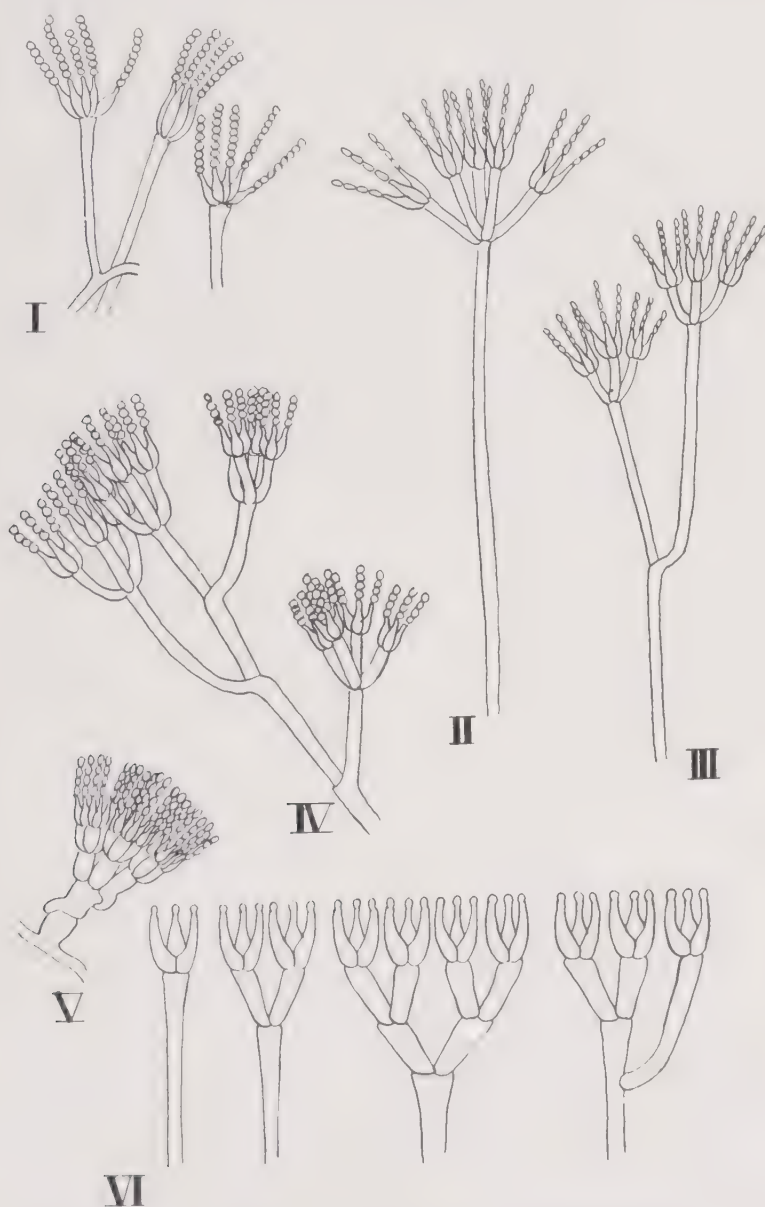


Fig. 233.—Varieties of penicillia. (After Henrici and Buchanan.) VI. General types: monoverticillata symmetrica; biverticillata symmetrica; polyverticillata symmetrica; asymmetrica.

Figures are diagrammatic. Actually, the mycelium of the ascomycetes is septate.

Citromyces. As a general rule the differentiation between aspergillus and penicillium can be made on the basis of the presence or absence of a vesicle, the terminal enlargement on the conidiophore. One mold, however, citromyces, presents the conidial arrangement of a monoverticillate penicillium but does have a vesicle. Thom classes this under penicillia while others place citromyces in a separate group between penicillia and aspergilli, see Fig. 231.



Fig. 234.—Penicillium teased on slide. Note brushlike conidiophore and free conidia.

Yeasts

Yeasts are forms between bacteria and the true molds. They are characterized by permanent unicellular growth without mycelium. One theory is that they have developed from molds by losing the power to produce mycelium. There are two general classes.

- (a) Those forming endogenous spores—Saccharomycetaceae—true yeasts.
- (b) Those without spores—Torulaceae—false yeasts.

Monilia, occasionally a pathogen, is transitional between the nonspore-forming yeasts and molds of the *fungi imperfecti*. It may appear in either of two forms, as yeast-like budding cells or with mycelium but in either case it produces no ascospores. The nonspore-forming yeasts or torulas may have arisen from spore-forming yeasts, merely having lost the ability to produce spores or they may have originated from transitional fungi such as the monilias by having lost the power to produce mycelium. There are, then, yeasts which form spores but no mycelium (saccharomyces); yeasts which form mycelium but no spores (monilia); and yeasts which produce neither spores nor mycelium (torula).

The ascomycetes possess the property of reproducing either by budding or sporulation. Upon losing the ability to produce mycelium they fall in the class saccharomycetes or true yeasts. These latter reproduce with budding

vegetative cells and by spore formation. Since they produce endogenous spores, often eight in number, the true yeasts are, strictly speaking, considered as members of the ascomycetes.

True yeasts, upon losing the ability to produce spores, fall in the class of false yeasts or torulas which consist of single cells without mycelium and which reproduce by budding only.

If the ascomycetes should lose the capability of spore production and reproduce by budding only, the resulting mold would fall in the class of monilias. The monilias produce mycelium and budding vegetative cells but no spores. They are *fungi imperfecti*.

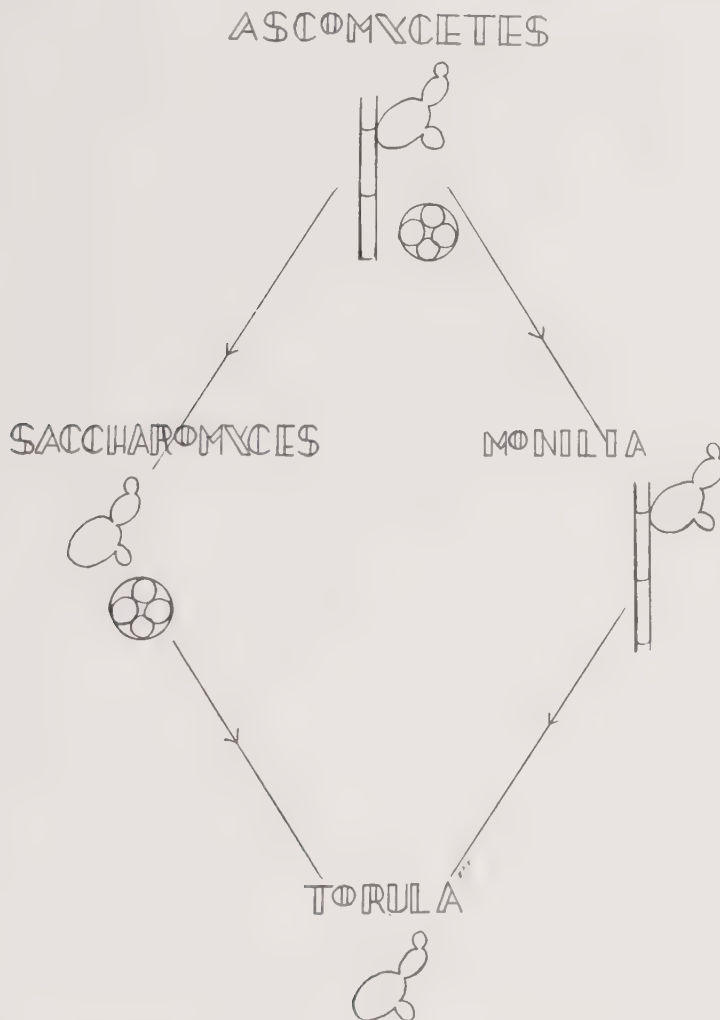


Fig. 235.—Interrelationship among the yeasts. Ascomycetes are capable of forming septate mycelium, budding forms and asci. If the ability to produce mycelium is lost but asci are still formed, the resulting fungus falls in the group, saccharomyces. If on the other hand the ability to form asci is lost while mycelium production persists, monilia results. Torula reproduces only by budding cells and may have been derived from saccharomyces by loss of ability to form asci or from monilia by loss of ability to form mycelium. (Adapted from Arthur T. Henrici, "Molds, Yeasts and Actinomyces," New York, 1930, John Wiley & Sons, Inc.)

Finally if these latter lose their ability to produce mycelium, the resulting organism will fall in the class torulas.

It should be understood that all *fungi imperfecti* are not of the appearance of monilia. They may appear as aspergillus, penicillium, or any of the other ascomycetes. The sole outstanding difference lies in the fact that ascospores have

not been observed. Indeed in the group of monilias, sexual spore formation is sometimes observed, as in *Monilia sitophila*, which is therefore one of the ascomycetes. *Monilia* may and usually does produce conidia as well as vegetative budding cells.

Torula therefore may have developed either from true yeasts which have lost their power to produce spores or from monilias (fungi imperfecti) which have lost their power to produce mycelium. Each of the two latter may have developed from the ascomycetes as outlined above.

The identification of yeasts is very difficult and sometimes impossible. Recently the use of sugar fermentation reactions has been very helpful in this respect.

Oidia and Monilia

While there have been some confusion and lack of uniformity in differentiating oidia and monilia, the present tendency is to class those which develop oidia between the joints of the mycelium as oidia, and those in which they develop only at the ends as monilia. *Oidium lactis*, in sour milk, is an example of the former.

Actinomyces

The actinomycetes are quite ubiquitous and represent a form of life between the schizomycetes or bacteria and the myxomycetes. They are represented by extremely fine mycelial growth less than one micron in diameter, nonseptate, with no visible nuclei and with conidia arranged in chains at the tips of the aerial hyphae. Oidia are formed frequently. The actinomyces is best known medically for its occasional infection of man but it is frequently found as a contaminant in laboratory culture media and might occasionally be found to be allergenic.

There are numerous varieties. The soil actinomycetes are easily cultivated while those pathogenic for man and animals are difficult to grow. Indeed, some have never been grown artificially.

The colonies of the actinomyces are small, white or gray with a powdery surface, usually very adherent to the medium. On plates they appear in either of two forms. The first is elevated in the center and irregular in outline, with pointed pseudopod-like projections from the edges of which furrows of varying depths run toward the central peak. The appearance rather suggests a miniature mountain top. The second type instead of being wrinkled toward the center is irregularly wrinkled in all directions giving a pock-marked appearance.

The colonies may be of almost any color. Not infrequently there is a brownish discoloration of the surrounding culture media, supposedly due to the production of melanin by an enzyme. Actinomycetes grow better on an alkaline medium.

Actinomycetes represent about 17 per cent of the microorganisms cultivable from the soil. They are responsible for a disease of potatoes known as "potato scab," a very common condition in which warty excrescences appear upon the surface of the potato.

With actinomyces as prevalent as it is, it is entirely possible that one might become sensitized to this mold although I have seen no such case.

Streptothrix is a fine branching filamentous mold belonging in the group of actinomyces and differentiated therefrom by the fact that in tissues it does not produce "clubs." I have seen one asthmatic whose sputum contained

tremendous amounts of streptothrix and who obtained maximum relief from her asthma after receiving iodides for the treatment of her streptothrix infection. Unfortunately we were unable to cultivate this mold.

The sputum of a chronic asthmatic should always be examined carefully for streptothrix and actinomyces. It seems probable that for this particular group of molds this is a more important examination than cultivation from the air. Fortunately iodides often act almost as a specific in relieving this type of infection.

Cladothrix and leptothrix have also been classed with the actinomyces. Actinomyces exhibits true branching and forms "clubs" in infected tissues. Streptothrix likewise exhibits true branching but does not form clubs. Cladothrix shows a form of false branching while leptothrix does not branch. The formation of clubs is not a reliable criterion and differentiation is therefore often not easy. Cladothrix and leptothrix are larger forms, actually bacteria, and probably should not be classified in this group.

Trichophyton and Related Organisms

This group of minute molds, while obviously present to some extent in the dust of floors, is usually isolated and identified from cutaneous lesions. After isolation trichophyton may be grown without great difficulty. We have to deal with two general types of invaders, the first, a saprophytic group growing in the epidermis or in the hair, and the second, the truly parasitic group, penetrating more deeply and causing definite inflammatory reaction. The former are usually a heterogeneous group of organisms belonging chiefly to the *fungi imperfecti*, the latter, a rather closely related group, the dermatophytes.

The accepted classification up to the present has been that of Sabouraud based on the localization of the infection.

Achorion grows in the hair and produces peculiar yellow crusts or scutula in the scalp. The disease is known as favus.

Microsporum, the organism responsible for tinea capitis, ringworm of the scalp, infects children predominantly. The mycelium invades the hair. The spores are formed on the outside of the hair. They are polyhedral. An epilated hair examined in a drop of 10 or 20 per cent sodium hydroxide shows the irregular clusters of polyhedral spores on the surface, with filaments of segmented mycelium within the hair.

Endothrix trichophyton invades the hair follicles. Both mycelium and spores are found entirely within the hair. *Ectothrix trichophyton* grows both in and on the hair and the spores are chiefly external but are arranged in rows, not in a mosaic as in microsporum.

Neo-endothrix trichophyton predominates within the hair but a few mycelial filaments and spores are also found on its surface.

The above organisms are responsible for ringworm lesions of the scalp, and involve chiefly the hairs. In examining an infected hair one must be especially careful to obtain the hair root since it is chiefly in the root that the mold is to be found. It is a waste of time to attempt to examine hair which has been broken off short of the root.

Lesions of the smooth skin are produced by the following.

Epidermophyton produces eczematoid lesions of moist areas, the groin, axilla, the web of the fingers and toes and the soles of the feet. The parasite is found in the epithelium, not in the hairs.

Endodermophyton likewise occurs in the skin, not in the hairs, and forms intricate patterns of concentric rings with pronounced scaling. It is a disease of the Far East and the Pacific Islands, not of the United States.

Microsporum produces the characteristic ringworm of the skin which we usually see outside hairy areas. The lesion consists in flat, reddish patches sometimes round, sometimes irregular, forming rings, and darker at the margins. There is a tendency to healing in the center. *Endothrix trichophyton* sometimes produces the same lesion.

Ectothrix trichophyton produces elevated plaques, round or oval, papulo-squamous, of a reddish color. Pustulation often occurs at the margin.

Ringworm, as it is commonly understood, is therefore usually due either to one of the trichophytons or to microsporum. It may occur in hairy areas or on the skin but in either case usually begins as an infected hair follicle. The term epidermophyton should be used in discussing the superficial skin lesions, tinea cruris, and eczema marginatum. This, in contradistinction to trichophyton infection, does not tend to heal at the center. Epidermophyton is observed microscopically in the scales of epidermis and appears as articulated filaments of mycelium, breaking up into chains of oidia.

The familiar fungus infection of the hands and feet, so-called athlete's foot, is usually due to a low-grade trichophyton infection although in about 20 per cent epidermophyton is responsible.

Microsporon furfur or *Malassezia furfur* is responsible for pityriasis versicolor (tinea versicolor). In hydroxide solution it appears in the scales of epidermis as short irregular strands of branched mycelium with numerous round spores of variable size. Attempts to cultivate it on artificial media have so far failed.

Need for a key for the identification of atmospheric fungi.—From the preceding discussion it is obvious that the allergist, attempting to identify air-borne fungi, whether the spores be on pollen slides or the fungus be growing on culture medium, will have little opportunity to follow the Saccardo classification, based upon characteristics rarely observed in routine cultures. A classification based upon characteristics of the asexual reproductive tissues may be used to much greater advantage. Buchanan's Key possesses this advantage.

Although the number of proved allergenic fungi is not great, it seems probable that, with these as with pollens, continued study will find many additions to the list. For this reason it seems desirable to have a comprehensive key for the identification of the majority of molds that will be encountered in air analysis. No such key being available Dr. Frederick W. Shaw, Professor of Bacteriology at The Medical College of Virginia, has prepared one for this volume. It appears in the following chapter.

CHAPTER LIX

KEY TO THE FAMILIES AND GENERA OF COMMON MOLDS

By

FREDERICK W. SHAW, RICHMOND, VIRGINIA

(ILLUSTRATIONS BY CLAIRE BARDWELL)

PART I

KEY TO FAMILIES

Conidia present

Vegetative mycelium generally without septa. Spores generally borne in a sporangium (spore case)-----MUCORACEAE

Vegetative mycelium with septa. Spores not borne in a sporangium.

Hyphae not united into definite bodies

Hyphae and conidia hyaline or bright-colored-----MONILIACEAE

Hyphae or conidia dark, generally both-----DEMATIACEAE

Hyphae united into definite bodies

Conidiophores sessile, round, flat-----TUBERCULARIACEAE

Conidiophores stalked, in heads or cylindric-----STILBACEAE

Conidia not present -----MYCELIA STERILIA

Use of the Key to the Families and Genera of Common Molds

Molds growing in Petri plates are first examined grossly, attention being given to the character of the mat, its color and its appearance when viewed from below through the culture medium. If the growth is loose, like cotton wool, search is made for aerial rhizoids, especially when the cover is removed from the plate. If present and if the mold touches the cover, these can be recognized as they are torn from their attachment to the cover.

A small portion of the mold growth is removed with forceps, placed in a drop of saline on a microscope slide, teased out somewhat and examined under the microscope. It may or may not be covered with a cover glass. Search is made for conidia, and for the reproductive tissues (sporangia and conidiophores), which are studied. The mycelium itself is examined, particular search being made for the presence or absence of septa.

With this and other information as indicated in the Key, identification can be made. Identification is first made by families. Thus, if spores are present and enclosed in a spore case and the mycelium is nonseptate the fungus belongs to the family Mucoraceae. If the spores are not enclosed in a case and the mycelium has septa separating the individual cells, the hyphae are not united into definite bodies and these and the conidia are hyaline or bright colored, we are dealing with the family Moniliaceae. If, with these same characteristics the hyphae or conidia are dark we are dealing with the family, Dematiaceae.

If conidia are not present one should bear in mind that longer cultivation may be followed by the appearance of conidia.

The family having been identified, one now determines to what section of the family the specimen belongs. The proper section (indicated by Roman Numerals) is determined in Part II. One then turns to the appropriate section in Part III, completing identification in the same manner. Arabic numerals preceding the genera correspond to their numbers in the illustrations.

Often this rather laborious method of identification can be materially simplified by a reversal of the process. One finds those illustrations which most nearly resemble the specimen being examined and traces the identification backward, establishing points of identity or dissimilarity.

PART II

KEY TO THE GENERA

Sections of Mucoraceae

Sporangia present

Of one kind

Of two kinds

Sporangia not produced

Turn to Section I

“ “ “ II

“ “ “ III

Sections of Moniliaceae

Conidia 1-celled

Hyphae little different from the conidia	..	“	“	IV
Hyphae sharply differentiated from the conidia				
Conidia capitate	..	“	“	V
Conidia not in chains	..	“	“	VI
Conidia in chains	..	“	“	VII
Conidia not capitate	..	“	“	VIII
Conidia borne more or less irregularly on simple or branched but not inflated or whorled hyphae	..	“	“	IX
Conidia borne on whorled branches	..	“	“	X
Conidia 2-celled or more	..	“	“	XI
Conidia 2-celled	..	“	“	XII
Conidia 3 or more celled	..	“	“	XIII
Conidia forked, radiate or stellate	..	“	“	XIV
Conidia spirally coiled	..	“	“	XV
<i>Sections of Dematiaceae</i>				
Conidia 1-celled	Turn to Section			XVI
Conidia 2-celled	“	“	“	XVII
Conidia 3 or more celled	“	“	“	XVIII
Conidia muriform	..	“	“	XIX
Conidia spiral, forked, stellate or convolute	..	“	“	XX
<i>Sections of Tuberculariaceae</i>				
Conidia hyaline or bright-colored	..	“	“	XXI
Conidia 1-celled	..	“	“	XXII
Conidia several to many-celled	..	“	“	XXIII
Conidia generally olive to brown or black	..	“	“	XXIV
Conidia 1-celled; hyphae always olive to brown or black	..	“	“	XXV
Conidia many-celled	..	“	“	XXVI
<i>Sections of Stilbaceae</i>				
Hyphae and conidia hyaline or light colored	..	“	“	XXVII
Hyphae or conidia dark	..	“	“	XXVIII

PART III

SECTION I

Sporangia of one kind

Sporangiophore simple or branched but not repeatedly dichotomous

 Sporangiophores produced from stolons; arise in clusters
 Sporangiophores arise from the nodes

 Sporangiophores arise from the internodes

 Sporangiophores do not arise in clusters, stolons not present
 Mycelium in air brown and thorny

 Mycelium in air not brown and thorny
 Mycelium metallic; suspensors spiny

 Mycelium gray or brown; suspensors smooth
 Sporangiophores simple

 Sporangiophores variously branched; sporangia borne on the lateral, circinate branches
 Columella constricted; sporangia pear-shaped

 Columella not constricted; sporangia globular

Sporangiophore repeatedly dichotomous

1. Rhizopus
2. Absidia
3. Spinellus
4. Phycomyces
5. Mucor
6. Pirella
7. Circinella
8. Sporodinia



FIG. 236. Air-borne fungi. 1. *Rhizopus*. 2. *Absidia*. 3. *Spinellus*. 4. *Phycomyces*. 5. *Mucor*. 6. *Pirella*. 7. *Circinella*.

SECTION II

Sporangia of two kinds; the primary many-spored; the secondary few spored

- | | |
|--|-------------------------|
| Primary sporangia with columella, secondary without | 9. <i>Thamnidium</i> |
| Both kinds of sporangia with columella | 10. <i>Dicranophora</i> |
| Wall of sporangium thickened and persistent above, thin and dissolving below | 11. <i>Pilaira</i> |
| Sporangiophore swollen beneath the sporangium | 12. <i>Pilobolus</i> |
| Columella absent | |
| Sporangiophores erect, branches tapering | 13. <i>Mortierella</i> |
| Sporophores creeping, branches not tapering | 14. <i>Herpocladia</i> |

SECTION III

Sporangia not produced. Conidia present in chains or clusters

- | | |
|--------------------------------------|-----------------------------|
| Conidia in chains | |
| Conidiophore not swollen at the apex | 15. <i>Piptocephalis</i> |
| Conidiophore swollen at the apex | |
| Conidiophore branched | 16. <i>Synecephalastrum</i> |
| Conidiophore not branched | 17. <i>Synecephalis</i> |
| Conidia not in chains | 18. <i>Chaetocladium</i> |

SECTION IV

Hyphae little differentiated from the conidia, at times absent

- | | |
|--|--------------------------------------|
| Conidia oval, spherical, or fusiform | |
| Conidia develop by breaking up of hyphae, or form chains on short, undifferentiated branches | 19. <i>Oöspora</i> (<i>Oïdium</i>) |
| Conidia on definite branches; mycelium distinct | 20. <i>Monilia</i> |
| Conidia fusiform, pointed at each end | 21. <i>Fusidium</i> |
| Conidia bacillar or cuboid | |
| Conidiophores well differentiated | |
| Conidia long, rod-like, truncate | 22. <i>Polysextalum</i> |
| Conidia short, cuboid, truncate | 23. <i>Geotrichum</i> |
| Conidiophores nearly obsolete; conidia cylindric | 24. <i>Cylindrium</i> |

SECTION V

Conidia not in chains; globose to ellipsoid (round to oval)

- | | |
|---|-------------------------|
| Conidia sessile; conidiophores unbranched with inflated tip | 25. <i>Rhopalomyces</i> |
| Conidiophores much less or not at all inflated at tip | |
| Conidia embedded in mucus; conidiophores simple | 26. <i>Hyalopus</i> |
| Conidia not embedded in mucus | |
| Conidia radiating from tip | |

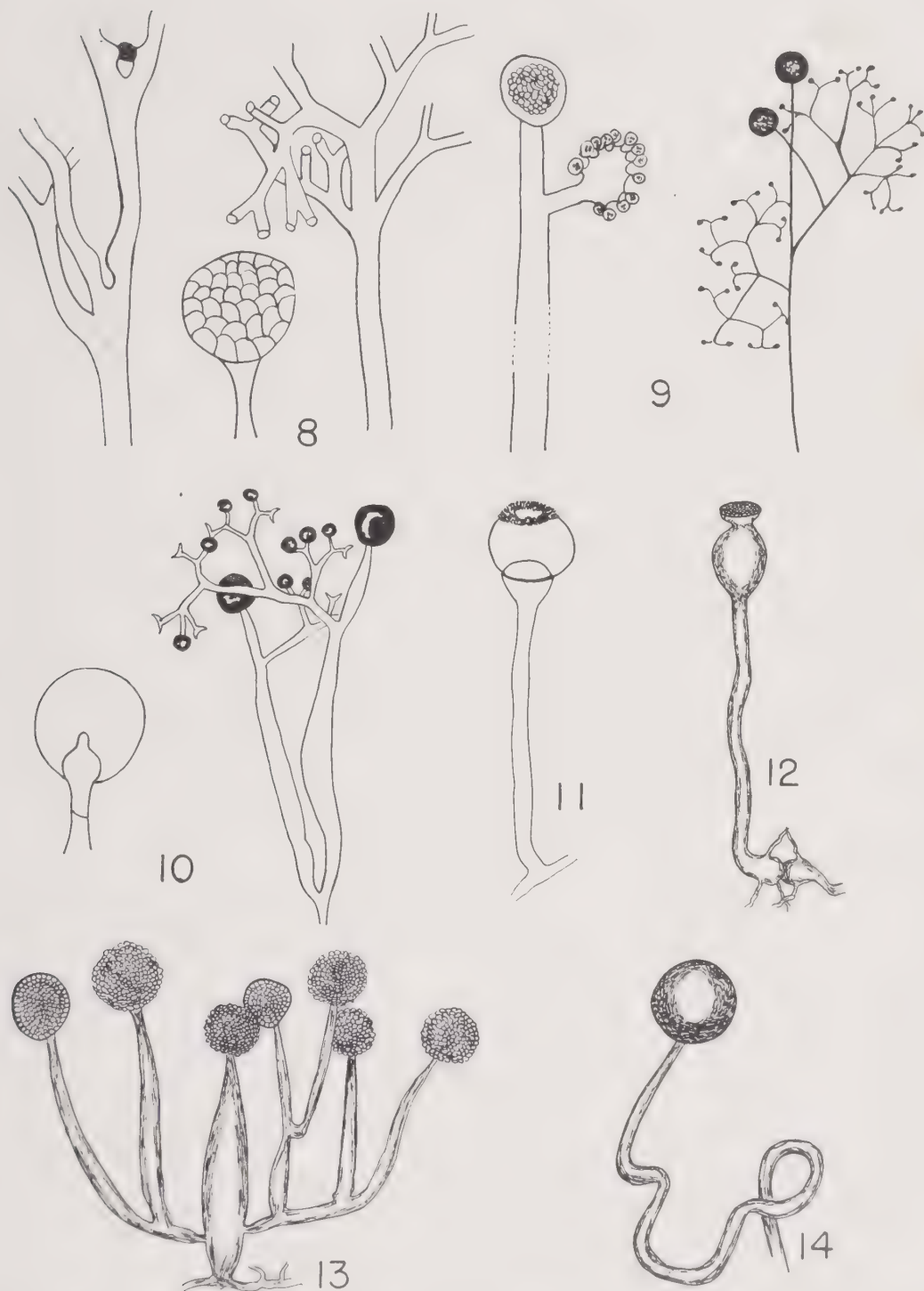


FIG. 237.—Air-borne fungi. 8. *Sporodinia*. 9. *Thamnidium*. 10. *Diceranophora*. 11. *Pilaira*. 12. *Pilobolus*. 13. *Mortierella*. 14. *Herpocladia*.

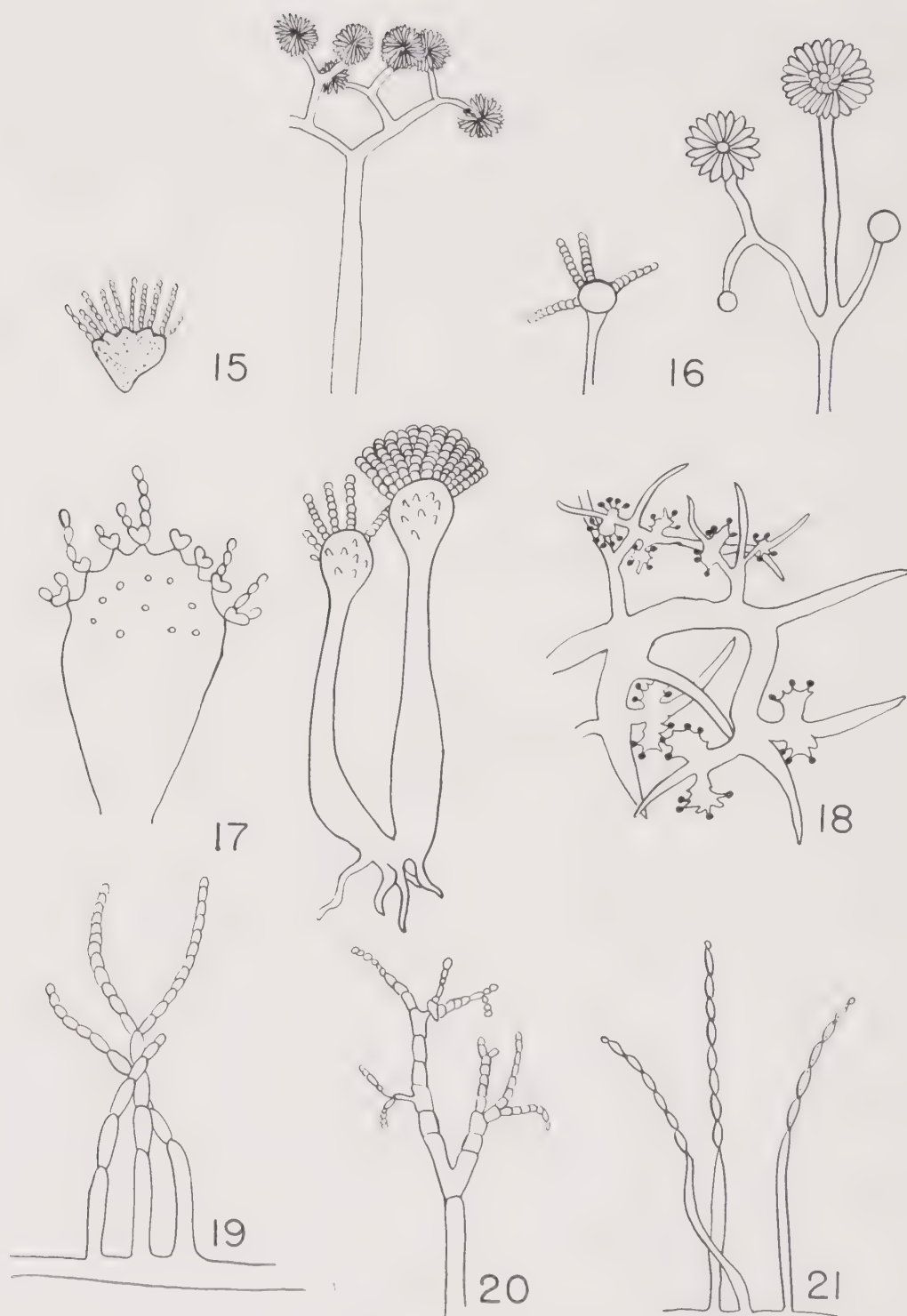


Fig. 238.—Air-borne fungi. 15. *Piptocephalis*. 16. *Syncephalastrum*. 17. *Syncephalis*. 18. *Chaetocladium*. 19. *Oöspora*. 20. *Monilia*. 21. *Fusidium*.

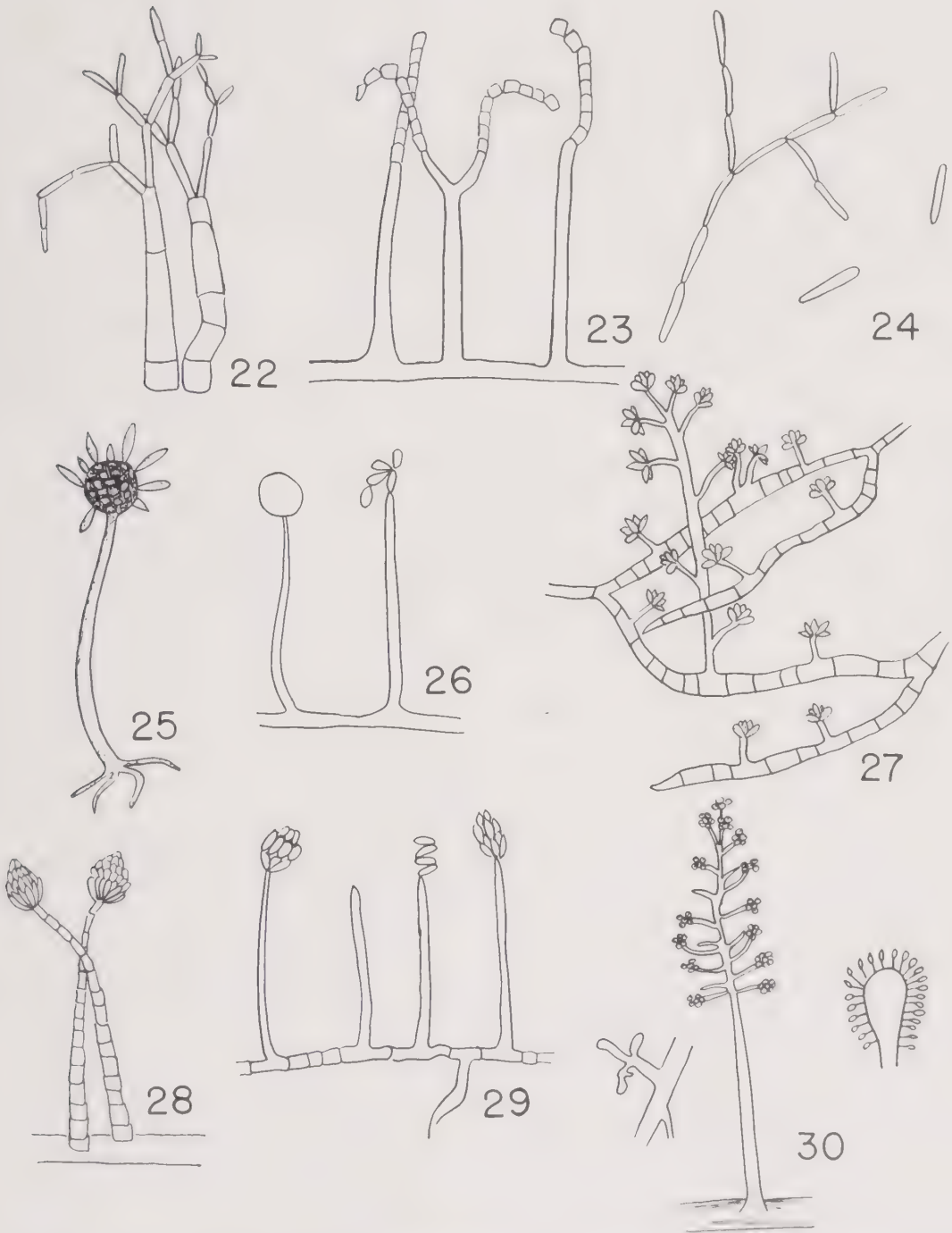


Fig. 239.—Air-borne fungi. 22. Polyscytalum. 23. Geotrichum. 24. Cylindrium. 25. Rhopalomyces. 26. Hyalopus. 27. Cylindrocephalum. 28. Haplotrichum. 29. Cephalosporium. 30. Botryosporium.

- Conidia cylindric
 - Conidia spherical
 - Conidia separating, head spherical; sterile hyphae long
 - Conidiophores branched
 - Conidiophore simple, with 3 or more heads of conidia on spines
 - Conidiophore tapering; head single on each tip
- 27. *Cylindrocephalum*
 - 28. *Haplotrichum*
 - 29. *Cephalosporium*
 - 30. *Botryosporium*
 - 31. *Trichoderma*

SECTION VI

Conidia in chains

- Conidiophore inflated at apex
 - Conidiophore simple
 - Conidial chains formed at the apex of sterigma
 - Sterigmata simple
 - Sterigmata branched
 - Conidiophore not inflated at apex
 - Conidia borne on sterigmata
 - Conidiophores with branches in regular whorls
 - Conidiophores branched or simple, whorls irregular, conidia not embedded in mucus
 - Conidiophores more or less regularly branched, without terminal swelling
 - Conidiophores unbranched, with a terminal tuft of sterigmata; terminal swelling present or absent
 - Conidia embedded in mucus
 - Conidia borne at apex of sterigmata
- 32. *Aspergillus*
 - 33. *Sterigmatocystis*
 - 34. *Amblyosporium*
 - 35. *Penicillium*
 - 36. *Citromyces*
 - 37. *Gliocladium*
 - 38. *Briarea*

SECTION VII

Conidiophores simple or branched; but no inflated or whorled hyphae

- Conidia grouped on inflated joints of the hyphae
 - Conidia produced on differentiated conidiophores
 - Conidiophores 2- or 3-branched
 - Conidiophores many times branched
 - Conidia single, terminal
 - Conidia loosely grouped about the apex
 - Conidia on short lateral conidiophores or irregularly on the hyphae
 - Conidiophores denticulate; conidia usually grouped
 - Apex denticulate, many spored
 - Conidiophores not denticulate
 - Conidiophores branched, vaguely branched
 - Conidiophores solitary; hyphae loose, cobwebby
- 39. *Nematogonium*
 - 40. *Haplaria*
 - 41. *Monosporium*
 - 42. *Botrytis*
 - 43. *Rhinotrichum*
 - 44. *Sporotrichum*
 - 45. *Acremonium*

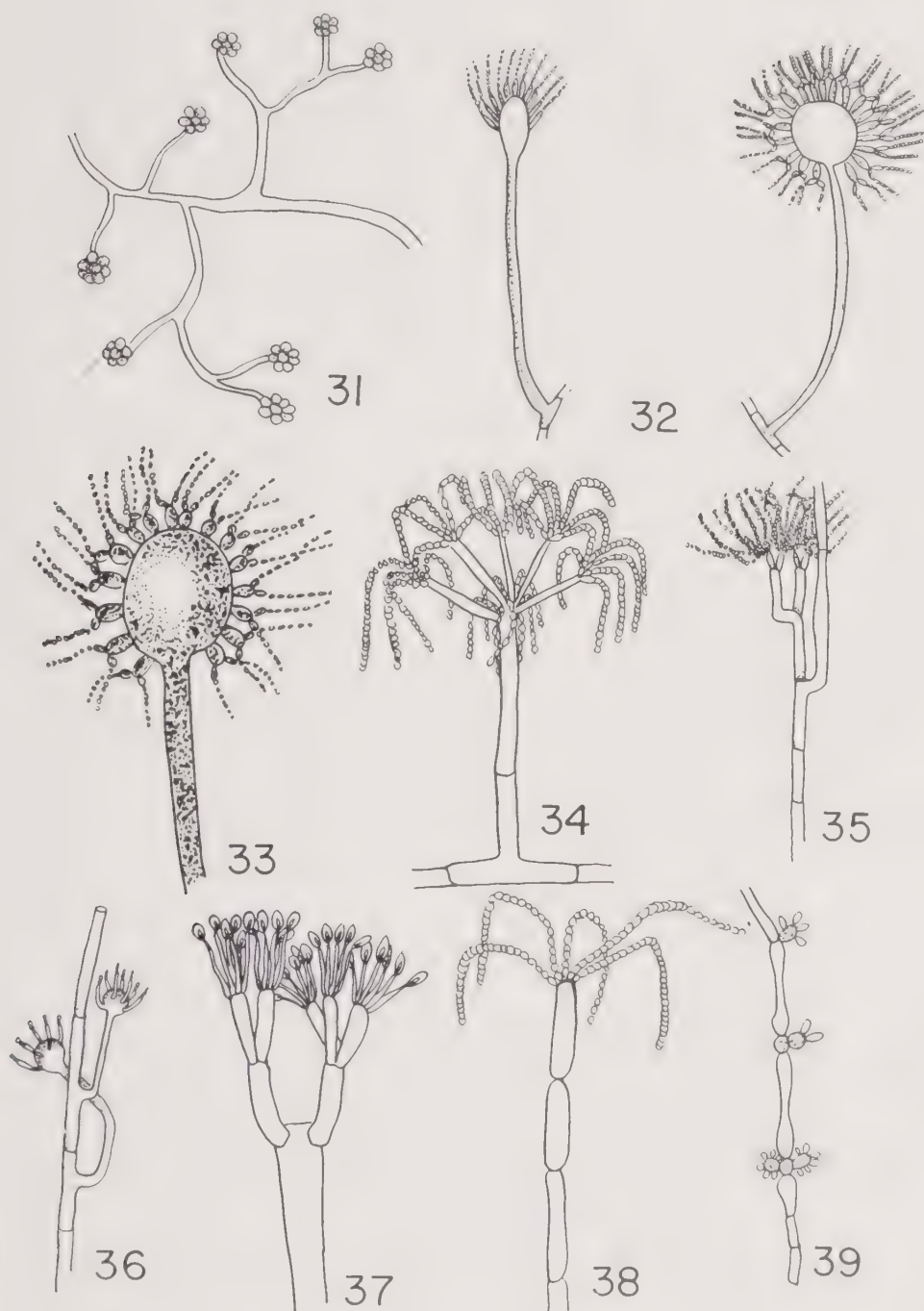


Fig. 240.—Air-borne fungi. 31. *Trichoderma*. 32. *Aspergillus*. 33. *Sterigmatocystis*. 34. *Amblyosporium*. 35. *Penicillium*. 36. *Citromyces*. 37. *Gliocladium*. 38. *Briarea*. 39. *Nematogonium*.

SECTION VIII

Conidiophores branched; branches in whorls

Conidia produced on flask-shaped end branches of the conidiophore

46. *Pachybasium*

Conidia not produced on flask-shaped branches

Conidia in terminal chains

47. *Spicaria*

Conidia not in terminal chains

Conidia produced in dense spikes

48. *Clonostachys*

Conidia not produced in dense spikes

Conidia embedded in mucus

49. *Acrostalagmus*

Conidia not embedded in mucus

Conidia spherical to ovoid

50. *Verticillium*

Conidia cylindric or elongate

51. *Aerocyndrium*

SECTION IX

Conidia 2-celled

Conidia in chains

Conidiophores simple; conidia develop as oidia

52. *Hormiactis*

Conidiophores branched; conidia ovoid

53. *Didymocladium*

Conidia not in chains

Conidia spiny; the two cells unequal

54. *Mycogone*

Conidia smooth

Conidiophores branched

Conidiophores whorled

55. *Diplocladium*

Conidiophores irregularly branched

56. *Diplosporium*

Conidiophores simple

Conidiophores inflated at joints and apex

57. *Arthrobotrys*

Conidiophores not inflated

Conidia arranged in spirals, singly

58. *Haplariopsis*

Conidia solitary, growing at the apex or in heads

Conidia in heads

59. *Cephalothecium*

Conidia solitary at apex

Conidiophores very short

60. *Trichothecium*

Conidiophores long

61. *Didymopsis*

SECTION X

Conidia 3- or more celled

Conidiophores short and not distinct from the conidia

Conidia in chains, cylindric; hyphae very short or obsolete

62. *Septocyndrium*

Conidia not in chains; conidia ciliate at apex and upper septum; conidiophores not inflated, sometimes obsolete

63. *Mastigosporium*

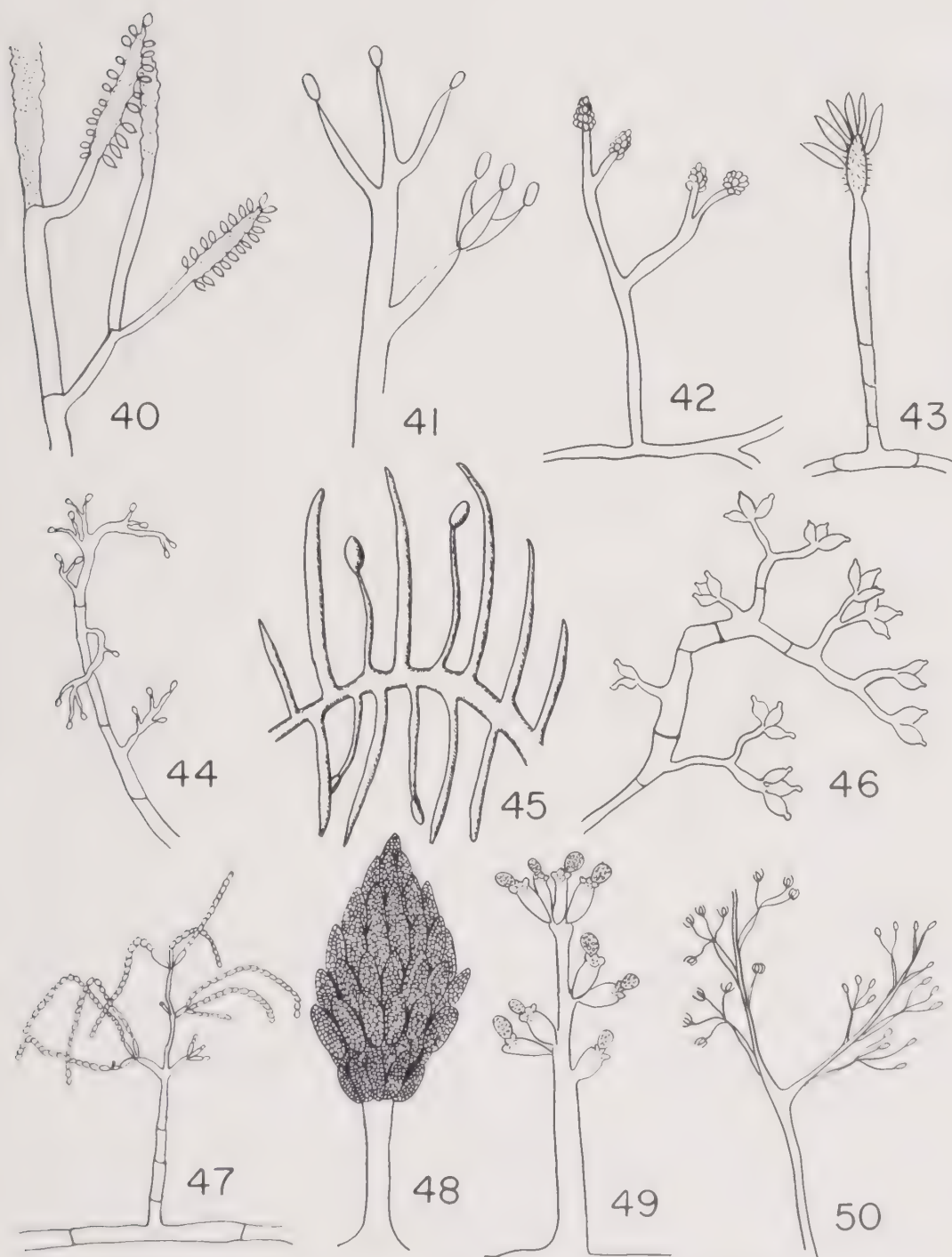


Fig. 241.—Air-borne fungi. 40. Haplaria. 41. Monosporium. 42. Botrytis. 43. Rhinotrichum. 44. Sporotrichum. 45. Acremonium. 46. Pachybasium. 47. Spicaria. 48. Clonostachys. 49. Acrostalagmus. 50. Verticillium.

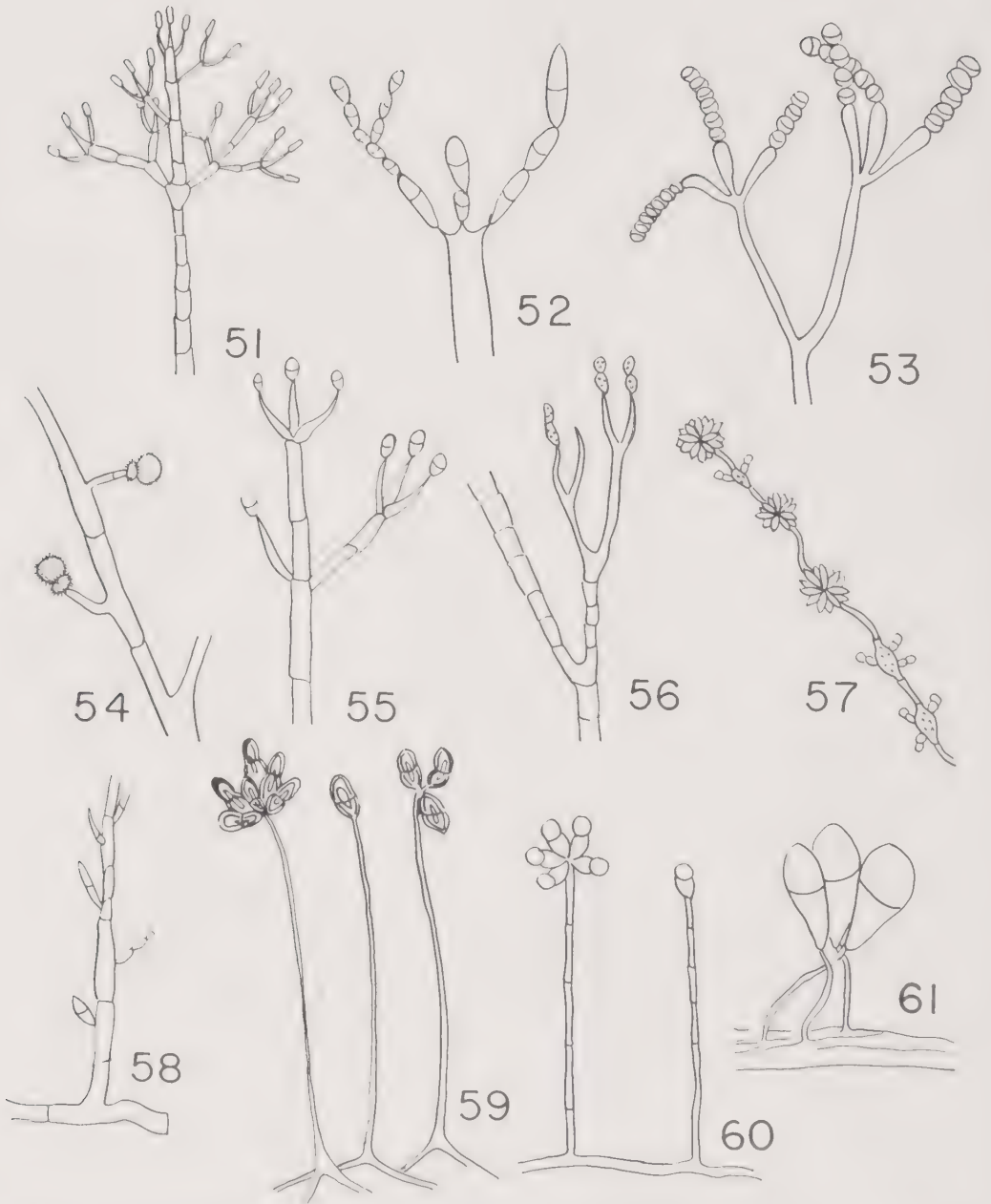


Fig. 242.—Air-borne fungi. 51. *Acrocylindrium*. 52. *Hormiactis*. 53. *Didymocladium*. 54. *Mycogone*. 55. *Diplocladium*. 56. *Diplosporium*. 57. *Arthrobotrys*. 58. *Haplariopsis*. 59. *Cephalothecium*. 60. *Trichothecium*. 61. *Didymopsis*.

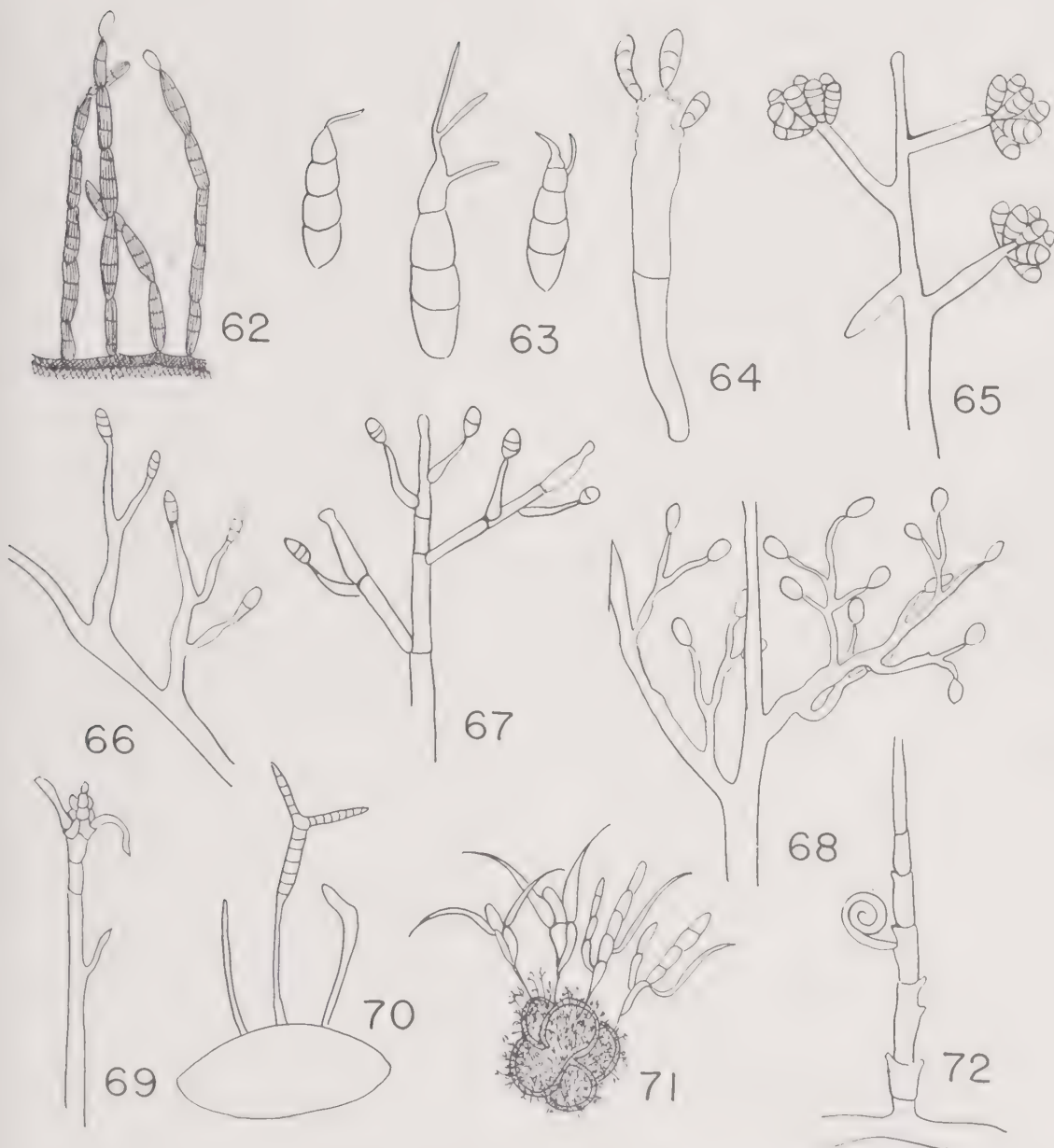


Fig. 243.—Air-borne fungi. 62. *Septocylindrium*. 63. *Mastigosporium*. 64. *Dactylaria*. 65. *Mucrosporium*. 66. *Monacrosporium*. 67. *Dactylium*. 68. *Blastotrichum*. 69. *Tetracladium*. 70. *Trinacrium*. 71. *Titaea*. 72. *Helicomyces*.

Conidiophores manifest and distinct from the conidia

Conidia in apical clusters; conidiophores not swollen

Conidiophores simple

64. *Dactylaria*

Conidiophores whorled

65. *Mucrosporium*

Conidia solitary

Conidiophores simple; sterile hyphae abundant

66. *Monacrosporium*

Conidiophores branched

Conidiophores whorled

67. *Dactylium*

Conidiophores irregularly branched; end branches single; conidia club-shaped to fusiform

68. *Blastorichum*

SECTION XI

Conidia forked, radiate or stellate

Conidia spherical to cylindric

Conidia with 2 or 3 divergent sterigma-like appendages

Conidia borne in the axils of these branches

69. *Tetracladium*

Conidia radiate

Conidia 3-radiate, rough

70. *Trinacrium*

Conidia 5-radiate of unequal size

71. *Titaea*

SECTION XII

Conidia spirally coiled

Conidia concentrically coiled

72. *Helicomycetes*

Conidia spirally twisted into a conic or ovoid tube

73. *Helicoon*

SECTION XIII

Conidia 1-celled

Conidiophores very short or scarcely different from the conidia

Conidia in chains; of one sort; hyphae dark

Conidial chains readily broken apart; conidia spherical to oblong

74. *Torula*

Conidial chains not readily broken apart; chains straight or nearly so

75. *Hormiscium*

Conidia not in chains but in heads or bunches, pear-shaped to flask-shaped

76. *Echinobotryum*

Conidia solitary, spherical to ovoid

77. *Coniosporium*

Conidiophores manifest and distinct from the conidia

Conidiophores simple or slightly branched; conidia lateral

78. *Dematium*

Conidiophores branched at apex; branched chains of Conidia

79. *Hormodendrum*

Conidia not in chains

Conidia in heads

Conidiophores simple with lateral basidia

80. *Periconia*

Conidiophores without basidia; conidia fusoid

81. *Acrotheca*

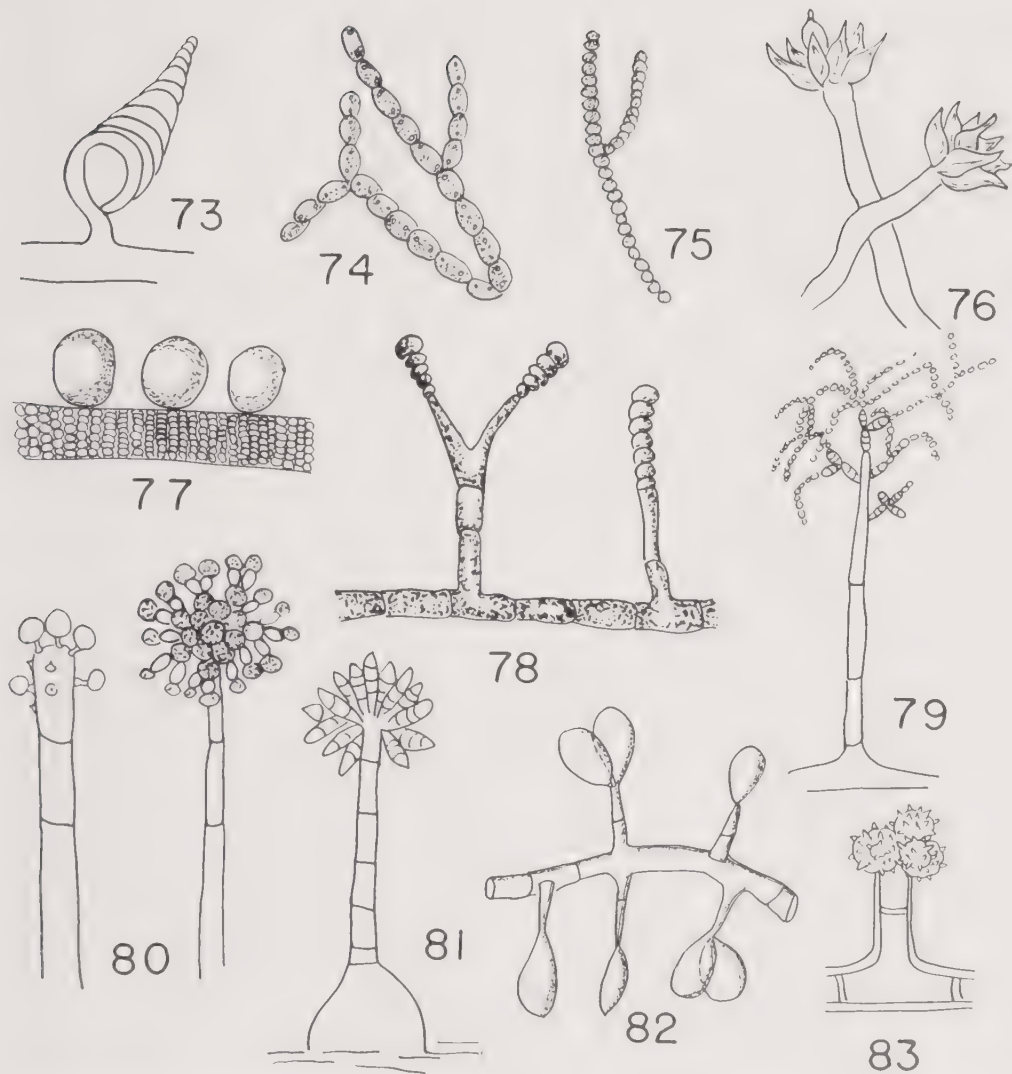


Fig. 244.—Air-borne fungi. 73. Helicoon. 74. Torula. 75. Hormiscium. 76. Echinobotryum. 77. Coniosporium. 78. Dematium. 79. Hormodendrum. 80. Periconia. 81. Acrotheca. 82. Acremoniella. 83. Zygodermus.

Conidia mostly single and borne at the apex

Conidiophores simple; conidia smooth, not in a dense mass; sterile hyphae without bristles

82. *Acremoniella*

Conidiophores swollen and branched; branches not curved; conidia spiny; hyphae creeping

83. *Zygodesmus*

SECTION XIV

Conidia 2-celled

Conidiophores very short; conidia solitary

84. *Dicoccum*

Conidiophores distinct; conidia not in heads

Conidia in chains, at least at first

Conidiophores erect; conidia in long chains

85. *Diplococcium*

Conidiophores somewhat decumbent; conidia in short chains of 2 to 3, often solitary

86. *Cladosporium*

Conidia not in chains

Conidiophores not flexuous or torulose, not inflated, usually short and little branched; conidia smooth

Conidia terminal only

87. *Fusicladium*

Conidia both terminal and lateral

88. *Scolecotrichum*

Conidiophores flexuous or torulose

89. *Polythrincium*

SECTION XV

Conidia 3-celled or more

Conidiophores very short or little differentiated from the conidia

Conidia in chains, without isthmi

90. *Septonema*

Conidia not in chains

Conidia cuspidate or setose

91. *Ceratophorum*

Conidia in bundles

92. *Stigmia*

Conidia solitary

93. *Clasterosporium*

Conidiophores long or distinctly differentiated from the conidia

Conidia arising from the interior of the hyphae; dark conidia in chains

94. *Sporochisma*

Conidia not in chains

Conidia in whorls

Conidia in terminal heads

95. *Aerothecium*

Conidia apical and lateral

96. *Spondylocladium*

Conidia not in whorls

Conidia smooth, elongate

97. *Helminthosporium*

Conidia prickly

98. *Heterosporium*

Conidia in chains, without isthmi

99. *Dendryphium*

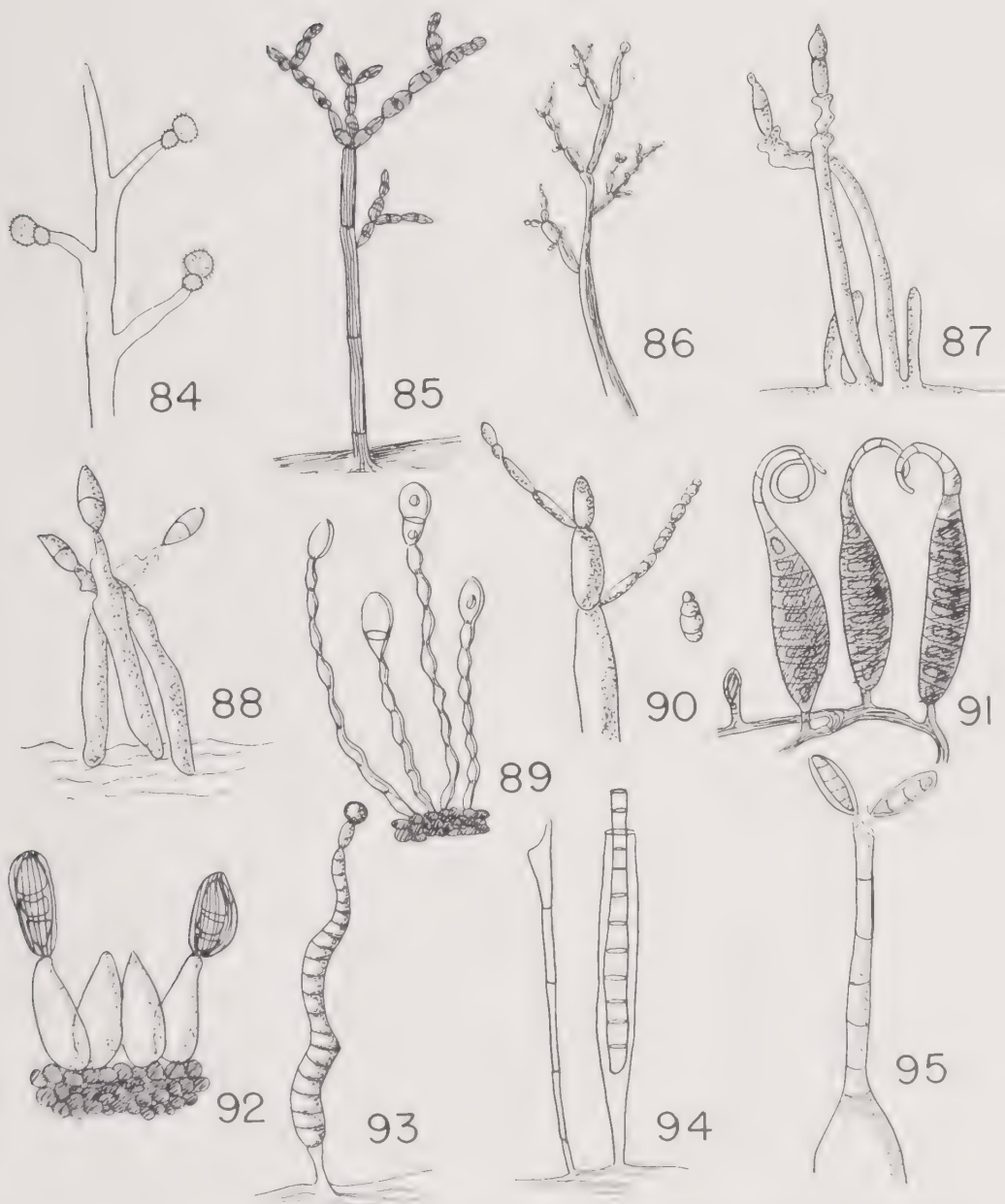


Fig. 245.—Air-borne fungi. 84. *Dicoccum*. 85. *Diplococcium*. 86. *Cladosporium*. 87. *Fusicladium*. 88. *Scolecotrichum*. 89. *Polythrincium*. 90. *Septonema*. 91. *Ceratophorum*. 92. *Stigmina*. 93. *Clasterosporium*. 94. *Sporochisma*. 95. *Acrothecium*.

SECTION XVI

Conidia muriform

Conidiophores short and not well differentiated from the conidia

Conidia not in chains

Conidia composed of parallel rows of cells

100. Dictyosporium

Conidia not composed of parallel rows of cells

Conidia muriform on short stalks

101. Sporodesmium

Conidia sarcinaeform, often coalescent

102. Coniothecium

Conidia in chains

103. Sirodesmium

Conidiophores long or distinctly different from the conidia

Conidia of two sorts, dark sarcinaeform and subhyaline

104. Sarcinella

Conidia alike

Conidia in chains, caudate

105. Alternaria

Conidia not in chains, solitary and apical

Conidiophores decumbent; conidia smooth

106. Stemphylium

Conidiophores erect; conidia terminal

107. Macrosporium

SECTION XVII

Conidia spiral, forked, stellate or convolute

Conidia spiral

108. Helicosporium

Conidia not spiral

Conidia long, filiform or vermicular, not hooked

109. Cercospora

Conidia 2-4 radiate of one sort

110. Triposporium

SECTION XVIII

Conidia 1-celled

Conidiophores and conidia present

Sporodochium with hairs or spines

111. Volutella

Sporodochium smooth, or rarely velvety

Conidia in chains

Sporodochium gelatinous, wart-shaped, sessile

112. Cylindrocolla

Sporodochium not gelatinous, dark

113. Blennoria

Conidia not in chains

Conidia produced within the hyphae, spherical

114. Endoconidium

Conidia produced on the outside of the hyphae

Conidiophores simple

115. Tuberculina

Conidiophores branched

Conidiophores dichotomous; forks without sterigmata

116. Dendrodoechium

Conidiophores and conidia not present, or imperfect

117. Illosporium

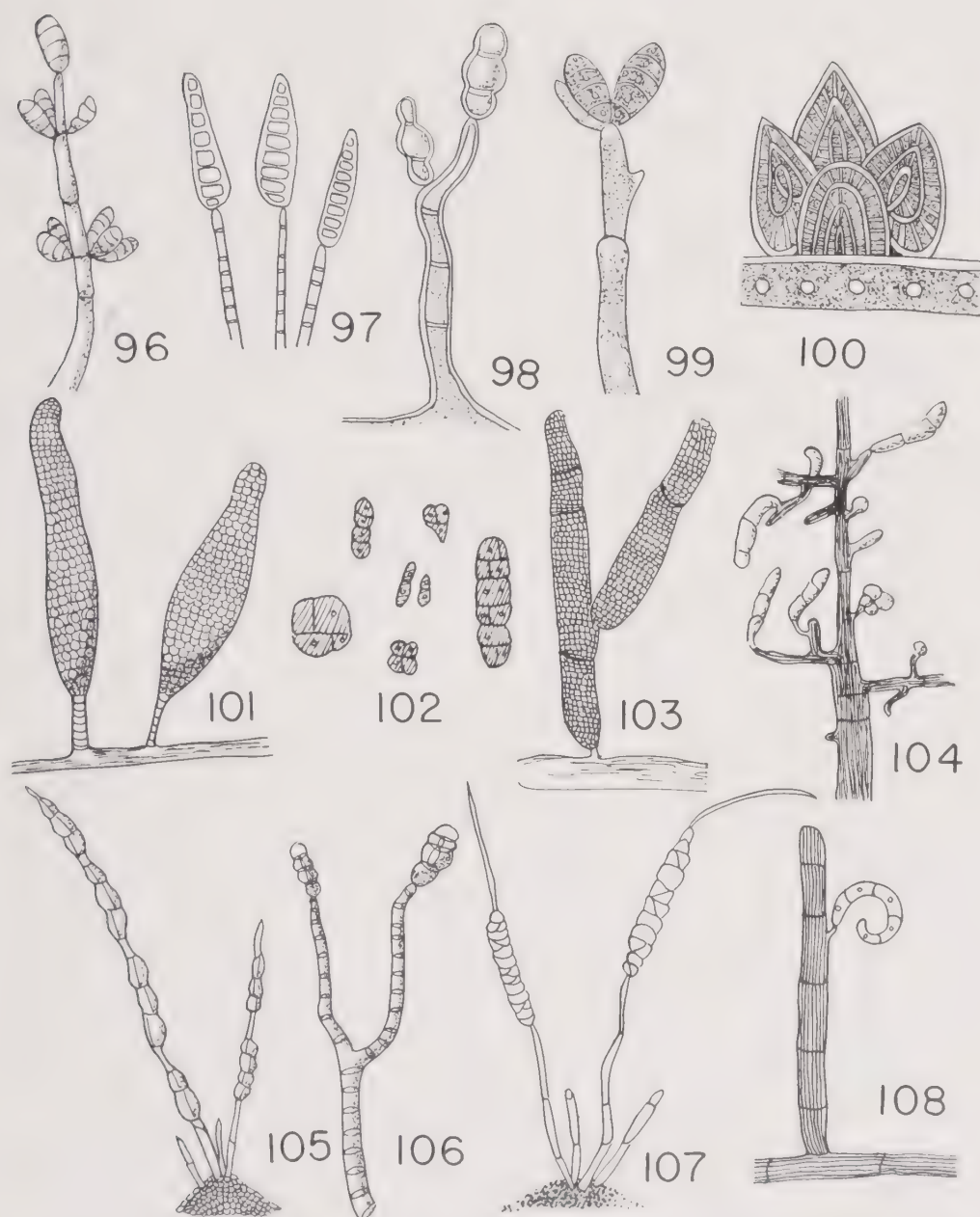


Fig. 246.—Air-borne fungi. 96. *Spondylocadium*. 97. *Helminthosporium*. 98. *Heterosporium*. 99. *Dendryphium*. 100. *Dictyosporium*. 101. *Sporidesmium*. 102. *Coniothecium*. 103. *Sirodesmium*. 104. *Sarcinella*. 105. *Alternaria*. 106. *Stemphylium*. 107. *Macrosporium*. 108. *Helicosporium*.

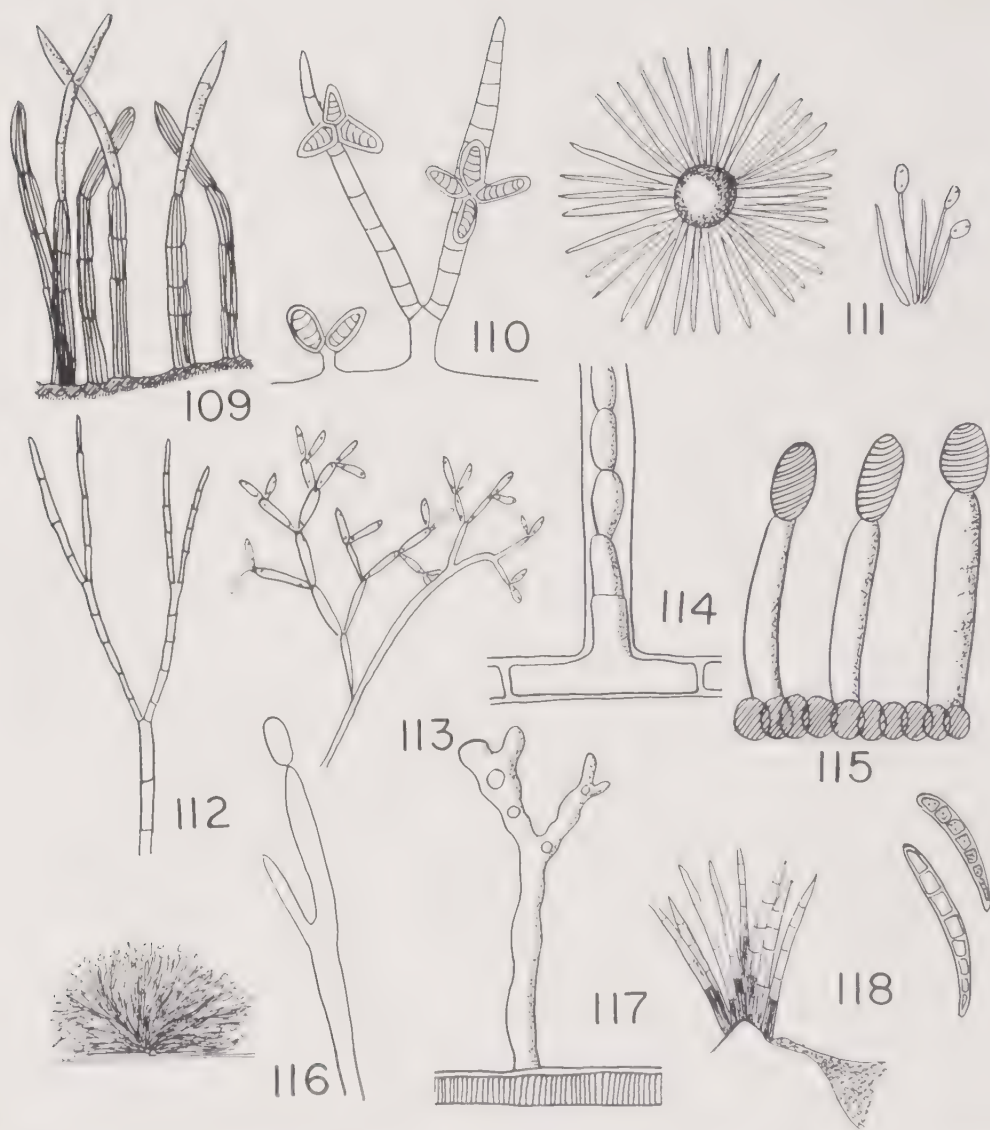


Fig. 247.—Air-borne fungi. 109, *Cercospora*. 110, *Triposporium*. 111, *Volutella*. 112, *Cylindrocolla*. 113, *Plennoria*. 114, *Endoconidium*. 115, *Tuberculina*. 116, *Dendrodochium*. 117, *Illosporium*. 118, *Fusarium*.

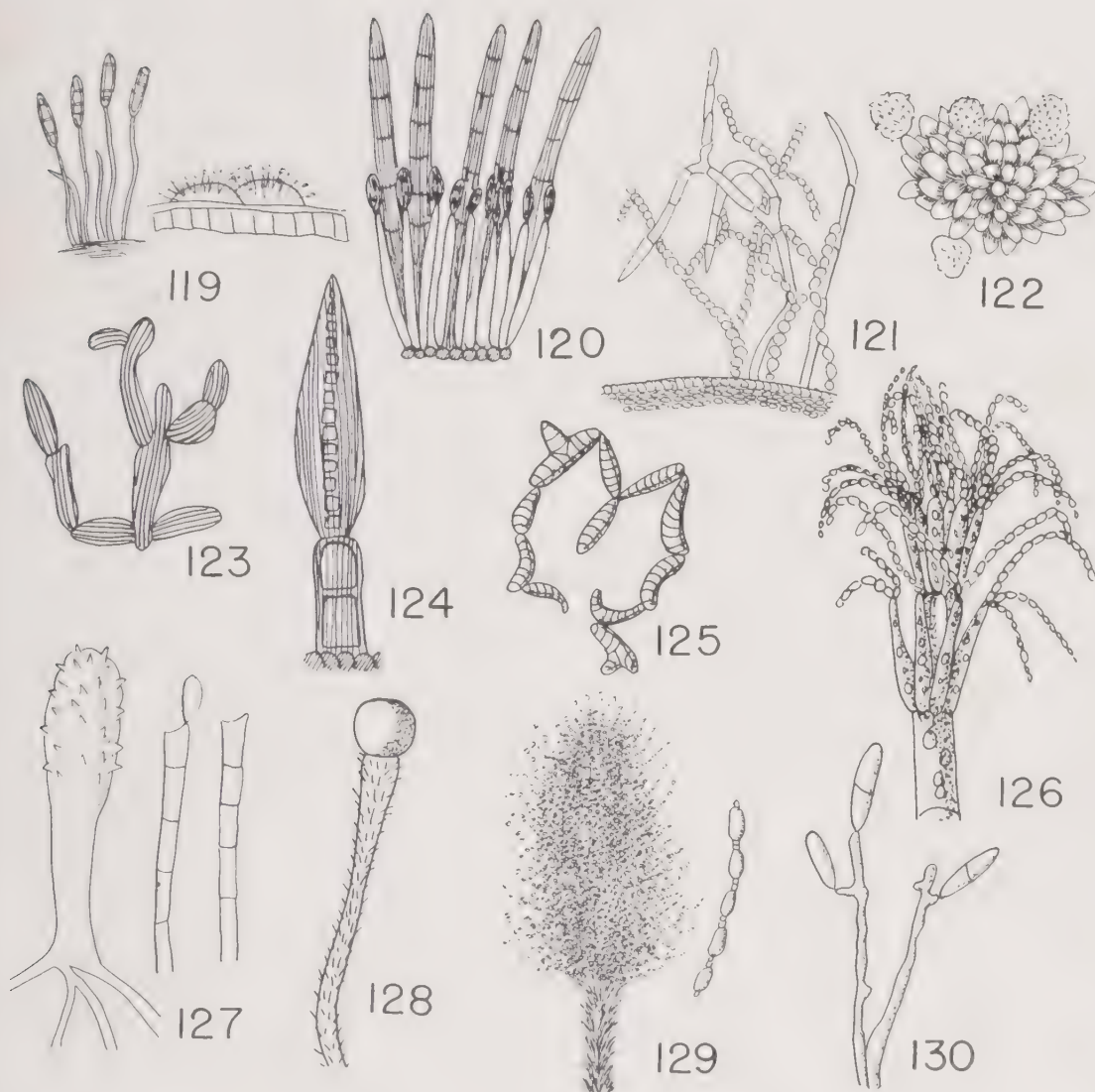


Fig. 248.—Air-borne fungi. 119. Bactridium. 120. Chaetostroma. 121. Periola. 122. Epicoccum. 123. Strumella. 124. Exosporium. 125. Trimmatostroma. 126. Coremium. 127. Stilbella. 128. Ciliciopus. 129. Stysanus. 130. Isariopsis.

Artist's acknowledgments. After Saccardo: Drawings 7, 19, 21, 23, 40 to 43, 45, 47, 50, 54, 57, 59, 61, 62, 64, 66, 67, 70, 71, 74, 76, 77, 80, 85, 88, 90 to 95, 97, 99, 101 to 104, 106, 108 to 110, 112, 113, 115 to 117, 119, 120, 122 to 124, 127, 130. After Lindau: 24, 26, 29, 30, 34, 37 to 39, 44, 46, 49, 51, 52, 55, 56, 58, 60, 63, 65, 68, 69, 72, 73, 81 to 84, 87, 96, 98, 111, 114, 118, 121, 125, 126, 128, 129. After Corda: 25, 28, 48, 89, 100. After Schroter: 3, 4, 10, 14, 16. After Van Teighem: 2, 9, 11, 13. After Brefeld: 15 and 18. After Bainer: 16. After Zopf: 12. After Winter: 17. After Riess: 22. After Harz: 27. After Bonorden: 8, 53. After Wendt: 20. After Chester: 107. The other drawings are original.

SECTION XIX

Conidia several- to many-celled

Conidia usually sickle-shaped

118. *Fusarium*

Conidia cylindric, very large

119. *Baetridium*

SECTION XX

Conidia 1-celled; hyphae always olive to brown or black

Sporodochium bristly

Conidia dark

120. *Chaetostroma*

Conidia hyaline

121. *Periola*

Sporodochium smooth; conidia spherical, rough

122. *Epicoccum*

Sporodochium wart-shaped; conidia ovate, somewhat bent

123. *Strumella*

SECTION XXI

Conidia many-celled

Conidia not in chains, not pointed

124. *Exosporium*

Conidia in chains

125. *Trimmatostroma*

SECTION XXII

Hyphae and conidia hyaline or light colored

Conidia 1-celled, spherical, elliptic or oblong

Conidia in heads or terminal

Conidia in chains; hyphae bound in an erect group with conidia above; no mucus; not downy

126. *Coremium*

Conidia not in chains; head not spiny

Conidia covered with mucus; single terminal head

127. *Stilbella*

Conidia without mucus; spherical to fusoid, terminal

128. *Ciliciopus*

SECTION XXIII

Hyphae or conidia dark

Conidia dark, 1-celled, spherical to elongate

Conidia in chains; stalk simple

129. *Stysanus*

Conidia 3-several celled, oblong to cylindric, in heads, not embedded in mucus

130. *Isariopsis*

GLOSSARY

Aerogenous.	Growing at the apex.
Apical.	At the point of any structure.
Bacillar.	Bacilliform. Rod-shaped.
Capitate.	Having a head.
Catenulate.	In part united as in a chain.
Caudate.	Tailed.
Ciliate.	Fringed with hairs.
Circinate.	Coiled into a ring or partially so.
Columella.	Sterile axile body within a sporangium.
Conidiophore.	A sporophore bearing a conidium.

Conidiospore.	Same as conidium.
Conidium (a).	Spores usually produced directly from the hyphae.
Constricted.	Drawn together; contracted.
Convolute.	Rolled round.
Cuboid.	Resembling a cube.
Cuspidate.	With α tooth.
Cylindric.	Elongated, with a circular cross-section.
Decumbent.	Reclining with the summit ascending.
Denticulate.	Minutely toothed.
Dichotomous.	Forked.
Ellipsoid.	Like an ellipse.
Embedded.	Surrounded in.
Flexuose.	Bent alternately in opposite directions; zigzag.
Fusiform.	Thick but tapering towards each end.
Fusoid.	Somewhat fusiform.
Globose.	Nearly spherical.
Hyaline.	Colorless or translucent.
Hypha (ae).	The thread-like vegetative part of a fungus.
Isthmi.	Connecting parts.
Manifest.	Evident.
Muriform.	Having both longitudinal and transverse septa.
Mycelium.	The vegetative portion of thallus of fungi, composed of one or more hyphae.
Nodule.	A small knot or rounded body.
Obsolete.	Wanting or rudimentary.
Oidia.	Conidia formed by segmentation of hyphae.
Oval.	Broadly elliptic.
Ovate.	Shaped like a longitudinal section of a hen's egg.
Persistent.	Remaining till the part which bears it is matured.
Radiate.	Spreading from or arranged around a common center.
Sarcinaeform.	Packet-like.
Septum.	Any kind of partition.
Sessile.	Without a stalk.
Setose.	Bristly.
Simple.	Consisting of one piece or of one series.
Sporangiophore.	A sporophore bearing a sporangium.
Sporangium.	A spore case.
Spore.	A single cell which is asexual and is capable of developing directly into a new plant.
Sporodochium.	A compact conidial body; mass of sporophores.
Stellate.	Star-shaped.
Sterigma (ta).	A stalk-like branch of a basidium bearing a spore.
Stolon.	A runner.
Subhyaline.	Somewhat slightly hyaline.
Suspensor.	Supporting cell or group of cells.
Tortuous.	Bent or twisted in different directions.
Truncate.	Cut off at the end.
Verticillate.	Whorled.

CHAPTER LX

FUNGUS ALLERGY

In 1925 Van Leeuwen of Holland, finding a woman allergic to feathers but not to kapok, directed her to sleep on a kapok pillow. She was relieved for a time but later experienced recurrent asthma. She was found still negative to kapok but when tested with an extract from her own kapok pillow she reacted positively. Something had happened to the pillow, making it different from other kapok pillows. This factor was found to be a mold. From this beginning Van Leeuwen investigated fungus allergy in Holland, finding it to be very common. In view of the dampness of the country, one would anticipate heavier mold exposure and consequently a higher percentage of fungus allergy than in the United States. This appears to have been the case although several investigators have found a rather high incidence in damp seacoast cities and in old houses with damp cellars and mildewed floor boards. Jimenez Diaz finds fungus allergy a factor of real importance in the maritime areas of Spain. Fraenkel (1938) found 16 per cent of asthmatics in Germany to be fungus reactive as against 53 per cent in England. Similar differences were observed in the reactions to bacterial test material (21 and 61 per cent). He attributes these facts to the greater humidity and higher incidence of respiratory infections in England.

Molds as allergenic excitants.—What are the molds, then, that have been established as inhalant allergenic excitants?

Mucor, *Penicillium*, and *Aspergillus* were incriminated by Van Leeuwen (1925), *Puccinia graminis* Pers. by Cadham (1924), and *Penicillium glaucum* Link and certain *Aspergillus* species by Hansen (1928). Others were gradually added. An undesignated species of *Alternaria* was reported by Hopkins as early as 1930. Others have been reported by a great many workers (Pratt, 1938; Halpin, 1939; Harris, 1941). Many of these probably are *Alternaria tenuis* Nees, as this species is widely distributed in the United States. *Alternaria humicola* Oudem and *Alternaria Mali* Roberts were mentioned specifically by Brown in 1936 and the closely related species, *Phoma conidiogena* Schnegg by Benham in 1931.

A large number of *Aspergilli* have been reported: *A. candidus* Link, *A. clavatus* Desm., *A. conicus* Blochw., and *A. flavipes* Thom and Church (Brown, 1936); *A. flavus* Link (Van Leeuwen, 1925); *A. fumigatus* Fres. (Van Leeuwen, 1925; Bernton, 1930; Lamson, 1936; Brown, 1936); *A. glaucus* Link-group and *A. hortai* (Brown, 1936); *A. Oryzae* Cohn (Brown, 1936; Leopold, 1936); *A. nidulans* Eidam and *A. niger* Tieghem (Van Leeuwen, 1925; Brown, 1936; Lamson, 1936); *A. parasiticus* Speare and *A. terreus* Thom (Brown, 1936); and *A. Sydowi* Thom and Church (Prince, 1934). Among the *Penicillia*: undesignated *Penicillium* species (Van Leeuwen, 1925; Brown, 1936; Lamson, 1936); *P. chlorophacum* Biourge, *P. chrysogenum* Thom, *P. cyclopium* Westl., *P. elongatum* Dierckx, *P. expansum* Thom, *P. italicum* Wehmer, *P. lanosum* Westl., *P. roqueforti* Thom, and *Citromyces* species (Brown, 1936). Among the *Mucorales*: *Mucor* species (Van Leeuwen, 1925; Cadrecha and Quintera, 1939); *M. plumbeus* Bon. (Flood, 1931; Lamson, 1936); *M. Mucedo* Bref. (Brown, 1936); and *Rhizopus* species (Conant et al., 1936); and *Absidia* (Waldbott et al., 1941).

Monilias and yeasts include *Monilia* species (Lamson, 1936); *M. albicans* Zopf. (Bernard, 1934); *M. silophila* Sacc. (Brown, 1936; Prince, 1937); yeast species (Taub, 1932; Harris, 1938); bakers' and brewers' yeast, *Saccharomyces cerevisiae* Hansen (Brown, 1936); and *Torula* (Waldbott et al., 1941).

Plant pathogens cited include maple bark fungus, *Coniosporium sorticola* (Towey et al., 1932); grain smuts (Brown, 1936; Harris, 1939; Wittich, 1939 and 1940); *Puccinia graminis* Pers. (Cadham, 1924; Wittich, 1940); and *Microsphaera Alni* Wint. (Alderson & Mason, 1941). A saprophytic *Cladosporium* (Bernton & Thom, 1937) and a tomato pathogen, *Cladosporium fulvum*, Cooke (Cobe, 1932), have also been reported. Animal pathogens include *Trichophyton* species (Wise & Sulzberger, 1930), *T. gypsum* Bodin and *Epidermophyton inguinale* Sab. (Brown, 1936).

Other fungi reported include *Chaetomium* (Feinberg, 1936; Lamson, 1936); *Cephalothecium roseum* Cda. and *Dicoccum asperum* Lindau (Brown, 1936); *Trichoderma* (Prince, 1937; Schonwald, 1941); *Helminthosporium* (Feinberg, 1936; Prince, 1937); *Fusarium* (Feinberg, 1936); and certain unnamed molds from mildewed awnings (Nichol, 1931).

Feinberg recommends the following mold extracts for diagnosis and treatment: *Alternaria*, *Hormodendrum*, *Aspergillus*, *Penicillium*, *Mucor*, *Chaetomium*, *Monilia*, *Trichoderma*, *Fusarium*, *Trichophyton* and smuts. The list should be modified from the standpoint of incidence in the atmosphere in the particular locality. The scratch reaction seems to give the closest approximation to clinical mold allergy.

Molds in houses and outdoors.—Early it appeared that the chief source of exposure was in damp climates and especially in damp houses. Paraphrasing Thom's statement that molds are the weeds of the culture room, Brown states that "molds are the weeds of the home." While this is true as the writer has repeatedly observed in the old mansions along the rivers of Virginia, more recent studies, especially by Feinberg and Durham, indicate that air-borne fungi may be of importance in dry climates, and outdoors as well as indoors.

TABLE LIX
MACQUIDDY'S STUDIES OF AIR STRATA

ELEVATION	BACTERIAL COLONIES	MOLD COLONIES	POLLEN PER SQ. CM.	WIND DIRECTION	VELOCITY
Average counts of three exposures				Surface SSW	12 MPH
3,000 feet	423	Innumerable	167	SSW	25 MPH
4,000 feet	36	Innumerable	38	SSW	24 MPH
5,000 feet	51	18	17	SSW	24 MPH
6,000 feet	2	9	11	SSW	23 MPH
7,000 feet	7	10	9	SW	26 MPH

NOTE.—Counts on plates exposed at one and two thousand feet were practically identical with those of plates exposed at three thousand feet.

With the airplane, studies of fungus, pollen and bacterial distribution in the upper layers of the air were made possible. Several were made by mycologists. MacQuiddy made one from the point of view of allergy (1934). His tables indicate the presence of bacteria, molds and pollen grains even at a height of 7,000 feet. As a matter of fact the more recent stratosphere explorations have shown the presence of molds at much higher altitudes.

Durham (1937) found that the highest prevalence of *Alternaria* was in the midwest corresponding roughly to the wheat belt. In 1938 he found the geo-

graphical distribution of *Hormodendrum* similar to that of the *Alternaria*. Prince and Morrow (1937) found high counts of *Aspergillus*, *Monilia*, *Penicillium*, *Helminthosporium*, *Cephalosporium*, and *Spondylocladium* along the Texas coast in the winter months. Since 1938 these latter authors have reported on surveys made through the central and southwestern states the chief findings being *Alternaria*, *Hormodendrum*, *Fusarium*, *Aspergillus* and *Penicillium*. Many regional and local surveys have been made which show many variations but those mentioned above are very widely distributed and most frequently causing clinical allergy.

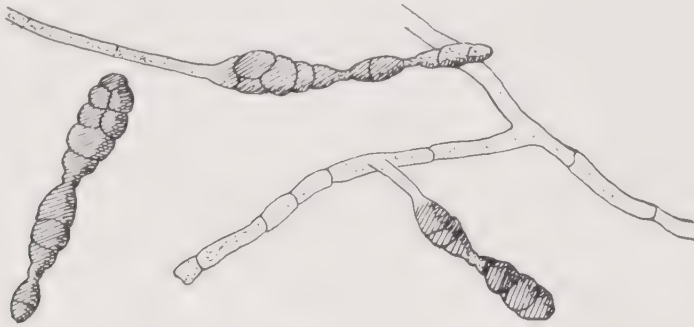


Fig. 249.—*Alternaria* spores. Showing mode of development from mycelium.

Durham (1938) has described an unusual shower of alternaria and hormodendrum spores which occurred throughout the eastern part of the United States on October sixth and seventh, 1937. On those days there were rapidly moving air masses spreading east and southeastward. Durham concludes that the crop of spores originated in southern Minnesota. Within 24 hours they had been carried as far east as New York City and as far south as Oklahoma City. The spore yield on pollen slides at remote stations was 100 times that of the mean daily count for the month, exclusive of the day of the storm.

Air-borne fungus spores may cause seasonal conjunctivitis. Simon (1938) has described such a case, reactive to alternaria and cladosporium, who gave positive skin and conjunctival reactions and was relieved following hyposensitization.



RELATIVE ATMOSPHERE CONCENTRATION OF ALTERNARIA SPORES IN REPRESENTATIVE AREAS

Fig. 250.

Mold surveys.—Feinberg and Little (1936) reported daily counts of the mold spores in the air, covering a twelve-month period. Determinations were made both by microscopic examination using the same method as in pollen counting, and by making cultures on suitable media. They found the most frequent air-borne spores to be those already listed as causing inhalant allergy; *alternaria*, *hormodendrum*, *cladosporium*, *penicillium*, *aspergillus*, *rhizopus*, *mucor*, *chaetomium*, *monilia* and *torula*. Others were encountered less frequently. They found, especially with *alternaria* and *hormodendrum*, the two fungi most intensively studied, that there is a distinct seasonal variation, the increase in Chicago starting in May, reaching a peak in September or October and returning to a low level in December and January. With pollens there is a period of low prevalence between the grass and weed seasons. This is not the case with fungi. They are increasingly prevalent in July and early August. This corresponded with clinical experience in that persons allergic to grasses and ragweed who continued with symptoms between the two seasons were often found allergic to *alternaria*.

Alternaria.—Durham next conducted a survey of the prevalence of *alternaria* spores on pollen slides exposed at forty weather bureau stations scattered over the United States. He found them in varying abundance in many parts of the country from May to November. Distribution was somewhat similar to that of ragweed, although it extended rather farther west toward the Rocky Mountain area, where the lessened rainfall is not as conducive to ragweed growth. Conversely it was less abundant along the Eastern Seaboard. Durham remarks that the *alternaria* belt corresponds roughly with the wheat or grain growing belt.

Alternaria is a mold with brown walled mycelium which produces the dirty gray or brown color in decaying vegetation.

Positive reactions.—Feinberg finds that *alternaria* gives positive skin reactions more frequently than other fungi, with yeast a close second. Others, in order, were *aspergillus*, *chaetomium*, *penicillium*, *monilia*, and *trichophyton*. *Alternaria* is also commonly found in house dust.

Lamson's order of frequency of positive reactions in Los Angeles was *alternaria*, *chaetomium*, *Aspergillus fumigatus*, *Aspergillus glaucus*, *Aspergillus nidulans*, *Aspergillus niger*, *monilia*, *Mucor plumbeus* and *penicillium*.

Yeast.—Yeasts according to Henrici are "fungi that permanently maintain a unicellular growth form, not developing mycelium." Asthma due to the ingestion of yeast was reported by Taub (1932). Brown (1932) observed positive yeast reactions when testing with fungi. Feinberg and Little (1935) found yeasts common in atmospheric mold cultures. Among 600 patients with inhalant allergy, 10.8 per cent reacted positively to yeasts. There appeared to be cross reactions among species and between yeasts and torulas. Crossed reaction between yeasts and monilias appeared infrequent.

Yeasts and monilias contain a polysaccharide fraction, apparently haptens in nature, which will produce anaphylactic shock in guinea pigs. Passive transfer of yeast reagin has been accomplished. Symptoms have been relieved by avoidance or desensitization and again produced following exposure. Yeast appears to be a true allergen.

Feinberg and Little consider bread the most important source of exposure. Each loaf contains approximately one-third ounce of pure yeast. Its antigenic capacity is not destroyed with baking. Yeast in cellophane envelopes in the center of loaves of bread, cooked for one hour at 450° F., was still allergenic.

The majority of white crackers are baked with yeast. Graham crackers, Ry-Krisp and most cookies and cakes have no yeast. Coffee cake, however, does contain it. Beer contains large amounts.

Vaughan has described frequent positive yeast reactions in inhalant allergies, especially those with perennial allergic coryza. Such persons usually react with an early wheal, often with pseudopods. Hyposensitization usually gives good results.

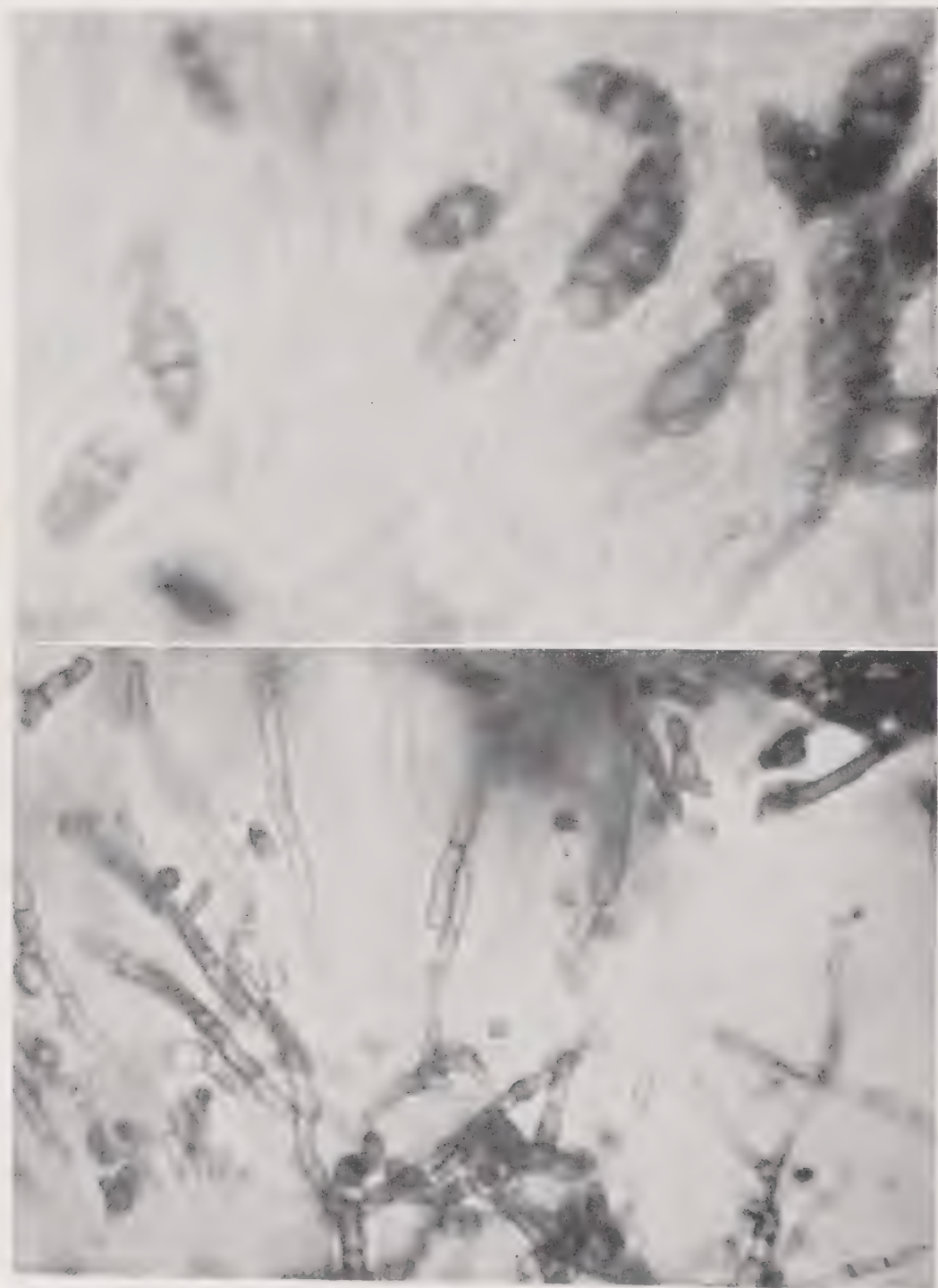


Fig. 251.—*Alternaria*. Upper figure: spores. Lower figure: note septate mycelium. (Low power.)

Cladosporium. **Hormodendrum.** *Cladosporium*, like *alternaria*, is responsible for the brown discoloration of decaying vegetable matter. A special variety, *Cladosporium fulvum*, grows particularly on the leaves of tomato plants. Cobe (1932) described asthma due to this fungus. Detweiler (1936) described a similar case in a man who grew hothouse tomatoes and experienced asthma each time he harvested them. Guba (1936) reported several cases in greenhouse tomato growers. *Cladosporium fulvum* according to Bernton is a special pathogenic variety, somewhat different from the commoner form which is often present in the air.

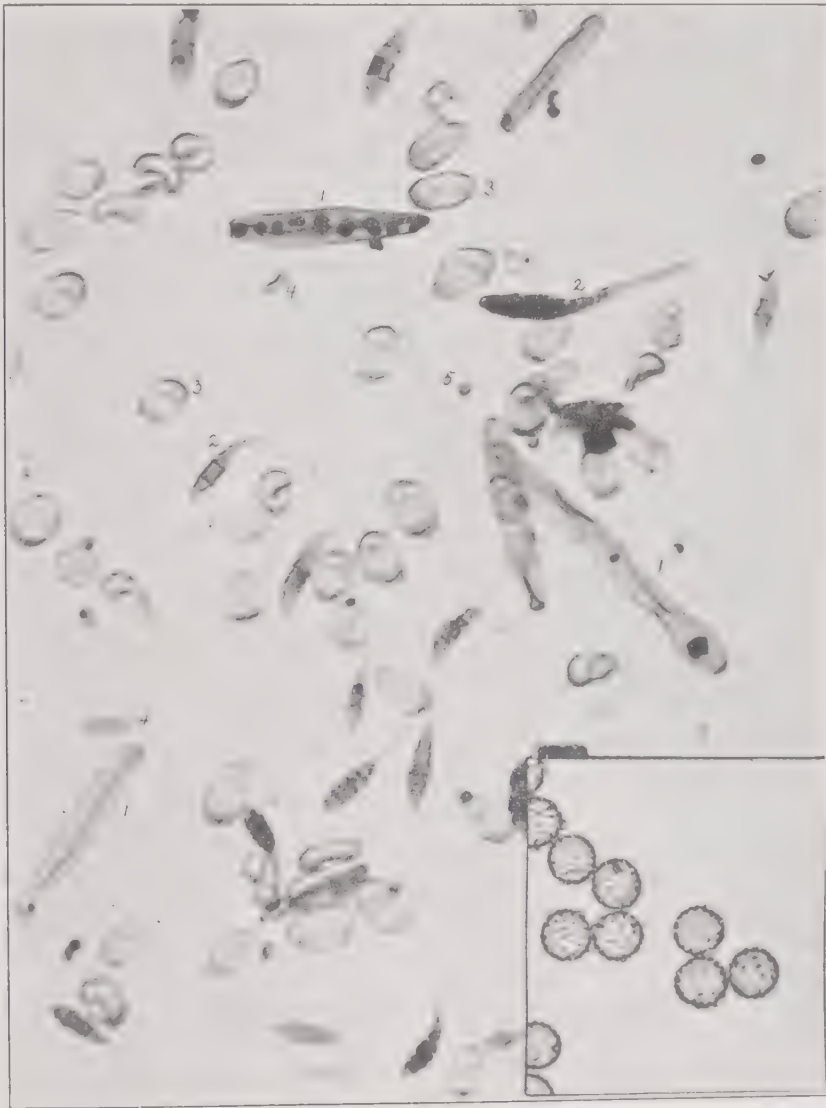


Fig. 252.—Miscellaneous fungus spores recovered from the apron of a binder during wheat harvest in Central Illinois. 1. *Helminthosporium*. 2. *Alternaria*. 3. Rust. 4. *Hormodendrum*. 5. Smut. Lower right: ragweed pollen for comparison. (Courtesy of Durham, O. C.: Incidence of Air-Borne Fungus Spores, *J. Allergy* 8: 482, 1937.)

The wide distribution of the latter is suggested by the fact that Meyer and Lindbergh found *cladosporium* 3,000 feet above sea level and well above the Arctic Circle. Bernton and Thom have described four cases of inhalant allergy to *cladosporium*.

Cladosporium and homodendrum are closely related or identical. Molds of this species with one-celled conidia are classed as homodendrum while those with two-celled conidia are termed cladosporium. Durham observed homodendrum (cladosporium) spores frequently in his national spore survey. Feinberg and Little found homodendrum as plentiful in the air as alternaria.

Mushroom.—This is primarily an ingestant allergen and is mentioned here only to emphasize that it, like the molds of cheeses, is a fungus. No one has as yet reported inhalant allergy to mushroom although Brown states that one mushroom may discharge as many as eighteen billion spores.

Molds as allergens. When it was suggested that molds might be responsible for allergy, a number of authors recommended caution in the acceptance of this concept. However, at the present time it appears safe to say that all of the requirements have been met. Positive skin reactions have been observed which can also be produced by passive transfer, indicating the presence of reagin. These reactions are of the early wheal type. Relief has been obtained by avoidance or hyposensitization and symptoms have been produced following subsequent exposure. The existence of the various molds in sufficient quantity has been demonstrated. The postulates of Cooke and Thommen appear to have been fulfilled. The substance which causes symptoms is the spore or reproductive element, corresponding to the similar allergenic substance of pollens and many of the foods. In this connection, Feinberg points out that for testing one should not use mycelium which is only feebly allergenic but spore extracts which are much more highly so.

Further evidence supporting the allergenic nature of fungi is seen in the specificity of the reaction. This is seen, for example, in the work of Lamson and Rogers on aspergillus, in which there was no evidence of complete crossed reaction between the four species of this mold. As with the pollens there is evidence of both group or family specificity and species specificity.

Rackemann (1938) reported three cases of allergy in greenhouse workers to tomato mold, *Cladosporium fulvum*, and claimed a high degree of specificity for this mold. Feinberg has done cross-desensitization by passive transfer and disagrees with the findings of Rackemann.

Frequency of fungus allergy.—Skin reactions to mold extracts vary in frequency with various observers as shown by the following table (Feinberg).

TABLE LX

AUTHORS	YEAR	TYPE OF CASES	METHOD OF TEST	NO. OF CASES	PER CENT POSITIVE
Hansen	1928	Respiratory	Intracutaneous	?	15
Balveat	1932	General allergy	Intracutaneous	480	0.8
Feinberg	1935	General allergy	Scratch	600	28
Lamson	1936	General allergy	Intracutaneous	1259	12
Schonwald	1938	Mold allergy	Intracutaneous	150	72 plus
Van der Veer	1937	General allergy	Intracutaneous	80	16
Rackemann	1939	Asthma	Intracutaneous	60	30
Prince	1939	Respiratory	Intracutaneous	150	68
Pennington	1941	General allergy	Intracutaneous	526	85
Waldbott	1941	Respiratory	Intracutaneous	841	69
Fraenkel	1938	Asthma (England)	Intracutaneous	131	61
		Asthma (Germany)	Intracutaneous	522	16
Feinberg	1942	Respiratory	Scratch	621	40.9

It is quite unlikely that these figures represent the actual amount of mold allergy. Positive reactions by the intracutaneous test may be of no significance or test extracts may be unreliable. Dependable figures upon the actual amount of clinical mold allergy are still lacking.

Therapeutic program.—The general principles are similar to those followed in other inhalant hyposensitization such as to house dust, tobacco smoke, orris root or pollens. The writer customarily starts with a high dilution such as 1:10,000 of a "concentrated" extract, increasing the dose until relief is obtained as is done with dust extract. One might determine nitrogen concentration and establish an initial dose. However, this is not necessary since our objective is not a standardized dosage but relief of symptoms. After symptoms have been relieved, the same program holds as for dust therapy.

The problem of avoidance is sometimes difficult. For example, patients living in old colonial houses in Williamsburg, Virginia, have moved to new

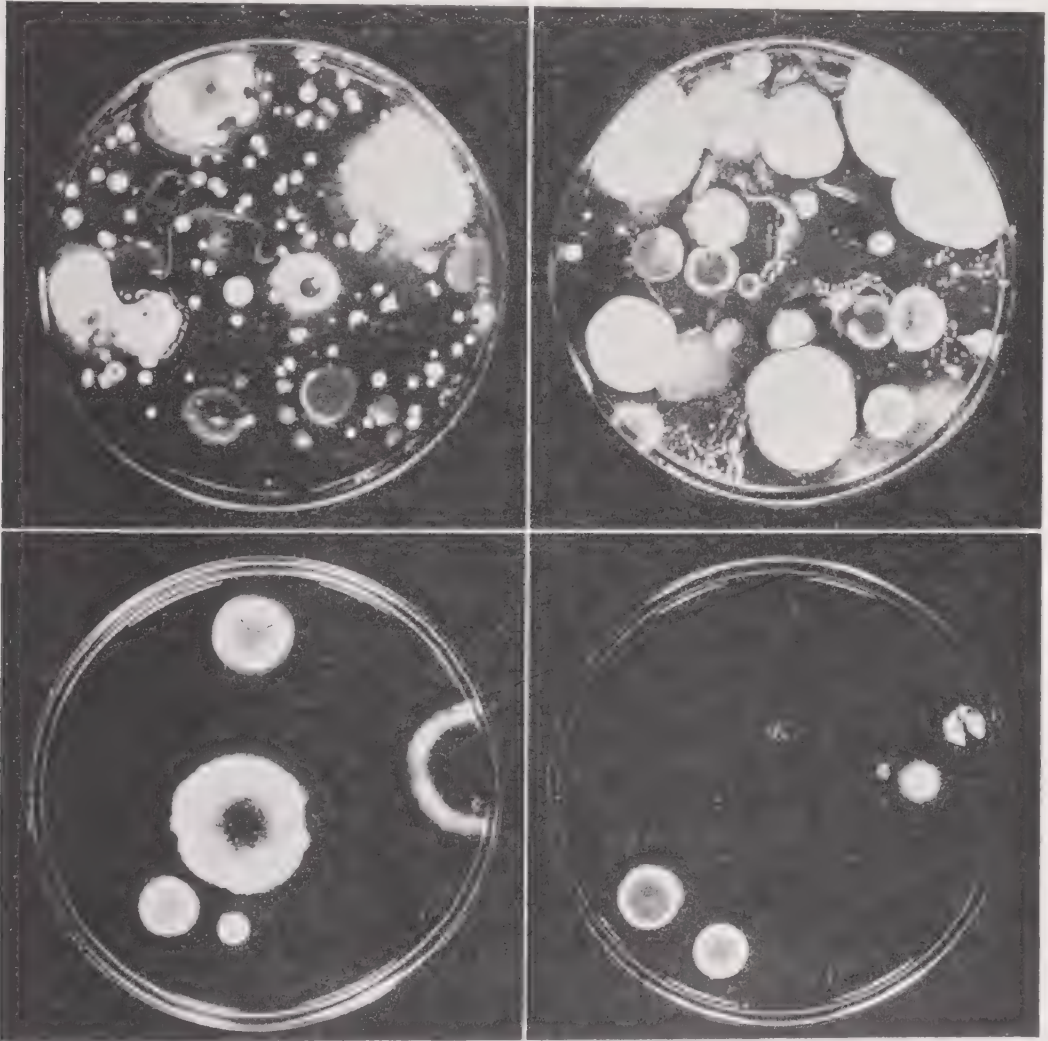


Fig. 253.—Atmospheric mold cultures on Petri plates. Length of exposure is important. Upper plates have been overexposed, precluding any possibility of pure culture transplants. They have some value in enabling one to determine varieties from inspection and microscopic examination, directly from the plate. Lower plates, exposed a much shorter time, developed isolated colonies from which material may be fished for pure culture.

homes in other cities but have carried the molds with them in their furniture, draperies, etc. Once they have been implanted in the new home, trouble may continue. Obviously, then, when the allergenic fungus is in the home the problem may involve not only a change of residence but also discarding of all upholstered furniture, rugs, and draperies that cannot be freed from fungi. In one family what appeared a catastrophe turned out a very fortunate occur-

rence. This family, one of whose members was mold allergic, was burned out of an old home and found it necessary not only to rebuild at another location but to completely refurnish the house.

In fungus hyposensitization as in other forms one should impress on the patient that the procedure will usually control a certain degree of exposure but that there are grades of inhalant contact beyond which therapy does not protect. Thus we have seen mold allergies who have been adequately relieved except when they go down cellar where fungus spores are extremely numerous.

It was natural that fungi should be suspected as possibly being the elusive allergen in house dust. Flood tested 18 dust-positive cases with 8 or 9 fungus extracts. He observed 8 positive reactions but produced an attack by spraying the throat with fungus extract in only one. Patients may be allergic to fungi in house dust but it has not been shown that house dust allergen is a fungus.

Results of treatment.—Feinberg reports that more than 80 to 90 per cent of mold sensitive patients are satisfactorily desensitized by the use of mold extracts. Pratt (1938) obtained relief in over 80 per cent, and Harris (1938) reported more than 75 per cent relief in 80 per cent of mold-sensitive patients. It would appear from the consensus of those most familiar with this work that the results are equally as good as with any other type of specific therapy.

Preliminary isolation of molds. This may be done following exposure on Sabouraud's or Czapek's media.

Feinberg and Little conducted their analysis of outdoor air by exposing Petri plates containing a modified Sabouraud's medium, horizontally, one foot outside a closed window on the fifth floor. Two consecutive plates were exposed, fifteen minutes each. They were then covered and allowed to incubate at room temperature for three or more days depending upon the rate of growth. Colonies were then identified both grossly and microscopically and counted. After some experience gross identification suffices in many instances.

Individual colonies are transferred to fresh agar plates or slants. The subcultures are incubated at room temperature or body temperature for from one to seven days, until the typical colored hyphae develop. It should be borne in mind that a mold is only feebly allergenic until the spores responsible for the characteristic color have developed. It is in the latter that the excitant is most abundant. Yeasts are best grown in sugar broth and beer worts with or without agar or gelatin.*

Feinberg's method of preparation of mold extracts.—Inoculate flasks containing one-half inch of special broth and grow at room temperature. Drain off broth and place pellicle in 95 per cent alcohol for 48 hours. Dry pellicle in air or over CaCl_2 . Grind to a fine powder. Five grams of the powder are defatted with ether and extracted with glycerine-Coca solution. Filter through paper then through a Seitz filter, test for sterility and label 1 to 20.

Formula for Broth

Distilled water	5,000	NaCl	25
Peptone (Armour)	50	Meat Extract	25
Autoclave. Filter. Add 100 Gm. Maltose. Autoclave.			

*Pure cultures may be obtained from the American Type Culture Collection, Georgetown University School of Medicine, Washington, D. C.

Formula for Potato-Dextrose Agar (for slants and plates)

Chopped potato	500	Boil until soft and pour off juice.
Water	1000	Filter if not clear. Then add
Dextrose	10	Heat until dissolved and make up
Agar	18	to 1,000 cc. Tube and autoclave.

Method of Hampton and Lowe.—A modified Waksman's acid-glucose-peptone broth was used, placing 200 to 250 cc. in one-liter Erlenmeyer flasks. These were inoculated and incubated in the dark at room temperature from two to four weeks. The pellicle was lifted gently, the broth poured off and the felt folded so that the upper surface was to the inside. It was then placed in a funnel containing sterile filter paper and washed several times with sterile normal saline. The wet pellicle was then ground in the sterilized chamber of a Universal food blender containing sterile Coca's fluid (without preservative). It was then transferred to a sterile Erlenmeyer flask and given a 48-hour period of germination. The extraction ratio was 20:1 based on the estimated dry weight of the pellicle. After germination phenol was added to make 0.5 per cent concentration, and the flask placed in the refrigerator for forty-eight hours more extraction. The suspension was then removed, pressed to separate the liquid and passed through a Seitz filter. It was then bottled and tested for sterility.

Method of Prince and Morrow.—These workers first used the pellicles which had been washed twenty times, dried slowly over CaCl_2 , then extracted in the ratio of 1:20. More recently they believe the extract has been improved by omitting the washing of the pellicle. The broth is simply decanted and the pellicle is frozen rapidly and dried by lyophilization. While the latter method seems to give an improved extract, work is being continued under the auspices of the Society for Mycological Investigation.

Preparation of trichophyton extract.*—Place in an Erlenmeyer flask, 100 cc. of dextrose broth (Difco) containing 3 gm. beef extract, 5 gm. peptone and 5 gm. dextrose. Sterilize in an autoclave for twenty minutes at 15 pounds pressure. Seed with a vigorously growing culture of trichophyton which is several weeks old. Allow to grow for at least three months. A thick layer forms on the surface. After three months transfer the pellicle to a sterile mortar, thoroughly grind with dry ice and kieselguhr to a fine powder. During this process add sufficient of the original culture broth to produce a thin gruel-like mush. Continue additions until approximately one-half of the broth is added. Add 0.5 per cent phenol as a preservative. Shake thoroughly for about one hour, after which incubate for 24 hours. After incubation add the remainder of the culture broth and again shake for one hour. Filter through Seitz. Deliver into sterile vaccine vials and test for sterility.

Sabouraud's Media.—**A. Conservation**

1. Peptone-----	30 gm.
2. Agar-----	20 gm.
3. Tap water-----	1000 cc.

B. Differential

1. Maltose, crude-----	40 gm.
2. Peptone-----	10 gm.
3. Agar-----	20 gm.
4. Tap water-----	1000 cc.

In the preparation of the differential medium, mix ingredients 2, 3 and 4, bring to a boil and then add the maltose. Filter if necessary. Autoclave each of the above media at 8 pounds for thirty minutes. Adjustment of reaction is not required.

*After Sulzberger and Brown.

The *differential medium* is for preliminary isolation while the *conservation medium* is for the maintaining of stock cultures.

Since cultural characteristics vary with slight changes of the medium, it is desirable to use the same ingredients as recommended by Sabouraud. These include "crude maltose of Chanut" and "granulated peptone of Chassaing" (Maison Cogit, 36 Boulevard St. Michel, Paris). Medium made of these ingredients is known as Sabouraud's "proof agar" (*milieu d'epreuve*). It might more accurately be termed "test agar." For routine work Henrici recommends 1 per cent Difco peptone and 5 per cent crude dextrose solidified with 1.5 per cent agar. Crude dextrose is preferred to purified sugar. Corn syrup may be used.

Czapek's Medium (Dox and Thom Modification).—

Sucrose-----	30.0	gm.
Sodium nitrate-----	2.0	gm.
Dibasic potassium phosphate-----	1.0	gm.
Magnesium sulfate (crystals)-----	0.5	gm.
Potassium chloride-----	0.5	gm.
Ferrous sulfate-----	0.01	gm.
Water-----	1000.0	cc.

This may be solidified with 1.5 per cent (15 gm.) agar. *Mucors* do not grow as well on this as on Sabouraud's media.

CHAPTER LXI

FUNGUS INFECTION WITH ASSOCIATED ALLERGY

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We have seen in the preceding chapter that Trichophyton and Monilia as well as other fungi are capable of producing respiratory allergy. There are many varieties of each, and a number are air-borne and present in dust, especially house dust. Members of the Trichophyton and Monilia families may also invade human integument, become parasitic. When this happens, allergic responses may occur.

Causative Organisms.—The superficial mycoses, particularly ringworm of the feet, are caused chiefly by *Trichophyton gypseum*, *Trichophyton purpureum*, *Monilia albicans*, and *Epidermophyton inguinale*. Dermatophytosis is rarely seen in children. Primary infection appears most commonly between the ages of 16 and 21 years (Lewis and Hopper, 1943).

Montgomery and Caspers' instructive and excellent article gives the following tabulation of causative organisms in cases of tinea of the hands and feet at the New York Skin and Cancer Unit between 1935 and 1943:

TABLE LXI

	FEET		HANDS	
	NO.	PER CENT	NO.	PER CENT
<i>T. gypseum</i>	1,016	65.4	36	12.2
<i>T. purpureum</i>	247	15.7	85	28.7
<i>M. albicans</i>	210	13.5	163	55.1
<i>E. inguinale</i>	44	2.8	6	2.0
Others	40	2.6	6	2.0
<i>T. unidentified</i>	(32)	--	(2)	--
<i>T. niveum</i>	(8)	--	--	--
<i>A. schoenleini</i>	--	--	(3)	--
<i>M. fulvum</i>	--	--	(1)	--
Total	1,557	100.0	296	100.0

Mechanism of Production of Disease.—Fungi, particularly Trichophyton, produce manifestations of disease principally through sensitization, through creating specific alterations in the direction of increased sensitivity; that is, through the production of allergic states, in a manner identical with or analogous to the sensitization mechanisms which operate in disease based on allergy produced by nonliving agents. No primarily harmful ingredient has been demonstrated in the organisms or extracts of Trichophyton or Monilia.

Trichophytin and Oidiomycin are harmless in individuals who have not been previously sensitized. There is usually no specific sensitivity to Trichophytin without a previous adequate exposure to the microorganisms. Sensitization does not occur through repeated exposures to Oidiomycin and/or Trichophytin. Trichophytin and Oidiomycin can produce no characteristic manifestations of disease unless a specific allergic sensitivity has first been established in the host. One may, therefore, conclude that a very large group of microorganisms produce disease, not necessarily through the elaboration of toxins, not necessarily through any primary harmful activity, but rather through their capacity to sensitize and to act as allergens (Sulzberger, 1940).

Occurrence on the Skin.—A number of careful studies have shown that, in the United States, a majority of adults constantly or sporadically harbor pathogenic fungi. These are found in the interdigital areas, the undersurfaces of the toes, the nails, and folds of the skin. These organisms may be present for varying periods of time without producing clinical evidence of disease. It is believed that activity and clinical manifestation of disease result from some alteration of local tissue immunity with or without an associated alteration of the general resistance of the host. Often the margin between the normal and disease is very narrow. Local resistance may be easily upset in some individuals by minor systemic and more readily by minor local influences.

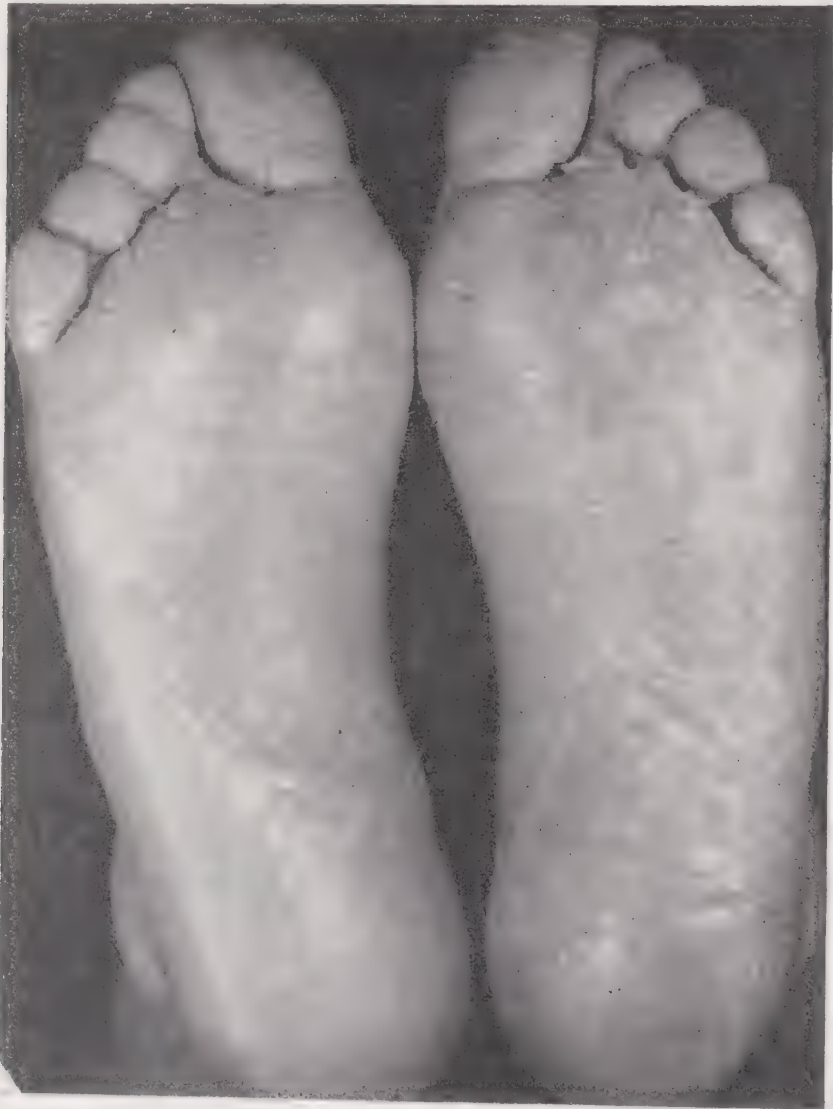


Fig. 254.—Chronic ringworm of the feet. (*Epidermophyton inguinale*.) Note the large flaky type of scales. Compare with *T. Purpureum* infection. (Courtesy Dr. Royal Montgomery.)

Clinical Picture.—The clinical picture of tinea of the interdigital areas of the feet and the major body folds may not be characteristic of fungus disease. Eczematous and eczematoid changes produced by the invading fungi plus secondary infection, and the eczematization of the skin caused by sensitization or the application of strong remedies makes a diagnosis of mycotic infection often

difficult. The following is a description of the clinical characteristics of ringworm of the hands and feet due to the four major causative fungi (Lewis and Hopper, 1943) and (Montgomery and Casper, 1945):

Trichophyton purpureum.—*Trichophyton purpureum* produces an eruption of the feet and hands which is characteristic of this particular organism. The infection on the foot may involve the soles, the sides, the dorsa, the toes, and/or the nails. The plantar surfaces are commonly involved. Itching frequently is a very annoying complaint. The entire sole of one or both feet is not uncommonly involved. The infection may be localized to small patches around the heel or on the ball of the foot. When the infection spreads along the sides of the foot and heel, a sharply margined erythematous border—"moccasin" effect—is given to the foot. The infected skin is dull red and slightly thickened. The scales are fine and branny. There is usually an absence of visible vesiculation. The infected skin has a tendency for decreased sweating. There is no tendency for central clearing. The infection of the undersurface of the toes and webs is similar to the infection on the sole. Interdigital maceration may occur. Fissuring is possible about the joints, especially if a hyperkeratotic reaction is present. Extensive involvement of the integument may occur.

The morphe of the eruption when the hand is involved is quite similar to that on the foot. The characteristics are the dull red color, with thickening of the skin, scaling, and absence of sweating, and with varying amounts of itching. The process is usually unilateral, but infrequently may become bilateral. The palmar surface of the hand, the sides, and palmar surface of the fingers and the nails are usually affected. Isolated irregular patches may be present about the dorsum of the hands and on the fingers. Redness of the skin with or without scaling may be noted over the joints of the hands.

Epidermophyton inguinale.—*Epidermophyton inguinale* according to Sabouraud involves the interdigital webs. It extends to involve the flexor surface of the toes. Maceration and severe scaling are characteristic of the infection in the interdigital webs.

The skin is decidedly scaly with the scales larger and flakier than those found in *Trichophyton purpureum*. Vesiculation may be present. The sole may be erythematous. If vesicles are present, on drying they become small brown macules and are easily lifted off. Most infections are limited to the toe areas, although the entire sole may be involved. A concomitant infection of groin and foot with the same organisms may occur.

Candida albicans.—The interdigital webs are the usual sites of involvement. The skin between the toes is bright red, moist and fissured at the base. Maceration is common. The borders of these lesions may have an overhanging collarette of scale. Usually bilateral involvement is found with the infection involving all interdigital webs. When the infection extends to the dorsum of the foot, the skin assumes a red, glazed, acutely inflamed appearance. Vesiculation is encountered infrequently.

Trichophyton gypsum.—*Trichophyton gypsum* commonly produces an inflammatory type of ringworm of the foot and infrequently of the hands. It is characterized by vesicles on the interdigital web, on the sole, the sides of the foot, and the bulb of the toe. *Trichophyton gypsum* uncommonly involves the dorsa of the toes and feet. Secondary eczematization due to overtreatment (primarily an irritant effect), sensitization, friction, maceration, or pyococcic organisms, in contrast, commonly involve the dorsa of the toes and feet and may overshadow the primary mycotic infection. When the interdigital infection

is in an inactive phase characterized by maceration, peeling, fissuring, etc., the inflammatory form may be indistinguishable from *Trichophyton purpureum* infection clinically. It has been pointed out that the web between the fourth and fifth toe is the most frequently infected site on the foot.



Fig. 255.—Acute inflammatory type of dermatophytosis (*T. gypsum*). Vesiculation is prominent. Vesicles on ball and arch of the same foot were free of fungi-dermatophytid. (Courtesy Dr. Royal Montgomery.)

Activity of this infection is associated with itching of varying degree, erythema, slight edema, and shortly thereafter vesiculation. The vesicles usually are deep-seated; at first they contain a clear viscid fluid. The fluid in two to three days becomes yellowish and turbid, and may become pustular. A microscopic examination of a potassium hydroxide preparation of the vesicle tops will reveal many elements of the fungi. Laboratory confirmation of the clinical diagnosis should be done in each case. The areas of vesiculation may extend peripherally or coalesce to form varying sized patches. Under favorable conditions the blister fluid may be absorbed, the tops of the blisters become brown, and the dead skin shed. Under favorable conditions spontaneous healing with remission takes place in dermatophytosis due to *Trichophyton gypsum* infection.

Dermatophytid.—Jadassohn (1911), before the Swiss Medical Congress, first described an eruption in patients with kerion. This eruption consisted of small, follicular elevations, occurring either in groups or diffusely, in large or small numbers; and which disappeared spontaneously. There was a symmetrical distribution; the trunk was the usual site, and often the extremities were involved as well. In some instances horny spikes, or spines capped the lesions and their appearance simulated lichen spinulosus. The work of Jadassohn, Bloch, Guth, and others of their school showed that these eruptions were expressions of cutaneous allergy due to the hematogenous spread from an inflam

matory focus on the scalp. Such a rash is designated as dermatophytid. The offending fungi sensitize the skin, and in such an altered terrain lesions developed which were in themselves sterile.

Dermatophytid in children has been observed to coincide with or follow a depilating dose of roentgen rays for tinea capitis. Infrequently it may result from therapeutic administration of trichophytin. Sometimes strong remedies applied topically cause a marked inflammatory change and have resulted in dermatophytid. In all instances the patients exhibited a strong reaction to intracutaneous test with trichophytin.

It was first thought that the eruption, dermatophytid, followed only deep fungus infections such as involvement of the scalp. Williams (1926) was the first to point out that secondary eruptions may follow infections of the interdigital webs, and infection of the groin area. Observation has not confirmed the belief that infection of nails may act in a like manner as a focus for dissemination of fungi and their products and the production of dermatophytid. Dermatophytid of the hands is characterized by symmetrically distributed vesicles which tend to localize on the sides of the fingers and the palms. The reason for this distribution for localization is not understood. Predelection for areas traumatized by occupation has been noted. A vesicular eruption of the feet—dermatophytid—may be caused by an active focus involving the interdigital webs. Here, as on the hand, fungi will not be found in the inflammatory vesicles.

Definition of a Secondary or "id" Type of Eruption:

Sulzberger has very ably outlined the criteria for secondary eruptions due to fungi. (Sulzberger, 1940.) They are:

1. An "id" is a secondary manifestation appearing in a specifically altered (allergic) tissue and produced by microorganisms emanating from a remote focus; and/or by the allergic products of such microorganisms.

2. An "id" occurs at a site distant both in time and space from the primary focus.

3. Distribution of the microorganisms and their products is usually by means of the blood stream. "Id's" differ from the original focus to a small degree in some cases and in others more markedly. This difference in the primary focus and the "id" is histologic, morphologic, mycologic, and immunologic.

4. A microorganism need not be demonstrable in the lesions of the "id." There must be, however, demonstrable previous exposure of the individual to the microorganism in question.

5. The secondary lesions may be evanescent in ringworm infection.

6. The skin of persons with dermatologic "id's" usually have a demonstrable specifically altered capacity to react to extracts of the microorganisms in question or to reinoculation with the microorganism. The altered skin reactivity may be hyperergic, hypoergic, or normergic. The following conditions, according to Peck (1930), are essential before the establishing of a diagnosis of an "id":

1. There must be a demonstrable focus and this focus must contain pathogenic fungi. On the feet in the majority of instances, the causative fungus is *Trichophyton gypsum*. Dermatophytid is almost never observed with *Trichophyton purpureum*.

2. The rash must be due to irritation of the primary focus by treatment or to a spontaneous inflammatory change. The intracutaneous test with Trichophytin reveals a positive reaction at the test site.

3. Fungi are usually not found in the lesion of dermatophytid.

4. The lesion disappears spontaneously when the focus has been eradicated. The only exception occurs when there are secondary eczematous changes and the rash continues because of sensitivity to other substances such as primary irritants.

Prophylaxis. In subjects without definite signs of clinical fungus infection, undecylinic powder proved to be the best available prophylactic agent against dermatophytosis of the feet. (Sulzberger, 1946.) Using the method of paired comparisons by applying two different medicaments, one to each foot of the same subject, the prophylactic value of undecylinic powder was tested against that of calcium propionate powder, talcum, 5 per cent thiourea in talcum and against unrelated controls. Similarly, results with Vioform powder 1 and 3 per cent, calcium propionate powder, and 5 per cent diodoquin powder were compared. In this series, from 3.7 to 10.8 per cent of subjects developed clinical infection with undecylinic powder prophylaxis during an observation period of over two months; concurrently the percentage for no treatment was 47.7; for calcium propionate powder 7.5; for talcum powder 23.1; for thiourea powder 19.6; and for U. S. Navy foot powder 23.4. A second group of paired comparisons, diodoquin powder and Vioform powder showed excellent results with only 2.4 and 4.2 per cent in each series developing infection during relatively short observation periods. As pointed out by Peek, Sulzberger, and others, their advantage over other antifungus preparations of equal effectiveness lies in their low irritating and sensitizing potential, even when used over long periods of time.



Fig. 256.—Dermatophytid of the hand and foot associated with a *T. gypsum* infection. (Courtesy Dr. Royal Montgomery.)

Efforts to prevent ringworm of the feet should always include cleanliness and proper foot hygiene, adequate ventilation of the feet, dryness, and the use of the proper footwear when engaging in athletic endeavors. Sterilization procedures are not recommended, since their value is questionable and their continued use favors sensitization.

Undecylinic powder and other fatty acid preparations are, therefore, recommended for prophylaxis for ringworm of the feet, groin, and the major skin folds. Acute attacks of dermatophytosis of the feet of adults are usually due to a flareup of a dormant infection and are not often due to picking up fungi from floors, shower rooms, the public beach, or bathing resort, bath mats, bathtubs and shoes. Peek and Schwartz (1945) could not culture fungi from shower room flooring soon after showers were taken by several hundred workers.

From answers by experienced dermatologists to a questionnaire by Sulzberger, Baer, and Hecht (1942) on the actual contagiousness of *tinea pedis* and *tinea cruris*, they concluded that conjugal and familial transmission of fungus diseases is either nonexistent or a great rarity. These recent studies are opposed to the beliefs and teachings of the past, for in the literature one can find reports of pathogenic fungi found by cultures of materials from floors, mats, and gymnasium apparatus, shoes, woods, and fabrics such as cotton, linen, silk, and wool.

Trichophytin and Oidiomycin.—Two important additions to routine testing materials are extracts from the trichophyton group and from *Candida albicans*. Although an immediate wheal reaction may be observed in *T. purpurum* infections, the characteristic positive is of the delayed tuberculin type, which may become very extensive with swelling, redness, soreness, and tenderness extending over an area the size of the palm of the hand and even with regional lymphadenopathy, from no more than 0.01 cc. of "undiluted" extract intracutaneously. These intense reactions may require several days for resolution, after which a small central area of desquamation and pigmentation may persist for several weeks. This occurs only in very pronounced reactions. However, a positive reaction may be sufficiently inconveniencing to the patient to warrant an explanation at the time of testing that the following day he may have a local reaction suggesting infection; that it has no such significance and may be improved by the local application of cold.

Pennington found that the trichophytin extracts prepared by Metz and by Lederle gave identical reactions when used in comparable dilution. Like Sulzberger, she found no evidence of crossed reactivity with oidiomycin (Lederle).

Dosage.—For a positive trichophytin reaction to be considered specific, it must occur with a dilution greater than 1:30 or 1:50 when given intracutaneously. For the *Candida albicans* reaction to be considered specific it must be positive in a dilution greater than 1:100 or 1:500.

Treatment.—Lewis (Lewis and Hopper, 1943) wisely stresses that the type of treatment should be indicated by the type of fungus present as determined clinically and culturally; by the presence or absence of allergic cutaneous response to fungi or topical applications, and by the morphologic state of the eruption on examination.

The basic concept that in the topical treatment of eczematous and eczematoid eruptions in which fungi play a role one is dealing with an eczematous eruption on a sensitization basis is worthy of emphasis. Such an eruption is best treated along the same lines as that of eczematous eruptions in general. The acute edematous, vesicular, weeping, denuded, eczematous response to fungi is best treated by wet dressings. In the subacute phase, powders, lotions, and pastes are indicated. In the late stages of the acute eruption and in the chronic with scaly, often hyperkeratotic, resistant manifestations, ointments and creams may be employed.

The principles of treatment (Wise and Sulzberger, 1937) are as follows: The production of mild desquamation so that fungi that are present in the stratum corneum are thrown off. A combination of a mild antiparasitic drug with a chemical which produces mild desquamation is often useful. When

indicated, the use of a few drugs that are considered efficient fungicides is beneficial. Soothing applications such as those which would be indicated in acute eczematous eruptions should be used for the more acutely inflamed reactions. This inflammatory reaction often tends to be curative (followed by a remission).

Fungi grow best and with greatest ease in areas where dead tissue and debris are most likely to accumulate. These are the folds of the body such as the interdigital folds, the area about the toenails, the intergluteal fold, the axillae, the groin sites, and the inframammary region. The best measures for reducing the quantity and/or the virulence of the fungi are agents which promote and increase desquamation and those agents which prevent heaping up of scales and debris.



Fig. 257.—Chronic dermatophytosis of the foot. (*Trichophyton purpureum*). The sharply margined border—"moccasin" effect—slightly thickened skin, fine branny scales, and dull red color are characteristic. (Courtesy Dr. Royal Montgomery.)

Therapeutic agents with a relatively high sensitizing or irritating index should not be used at all or employed with the proper caution. The physician should become acquainted with a few simple remedies and learn their potentialities, their indications, contraindications, and limitations. This is preferable to the employment of numerous medications with many of which he is unfamiliar. It is wise to acquire the ability to detect the initial phases of irritation and sensitization from topical applications and secondary infection which complicates dermatophytosis.

In general the skin is as likely to be irritated or exemplify polyvalent sensitization in an individual with an acute dermatophytosis and an extensive dermatophytid as is the patient with an extensive contact dermatitis due to plants or to sulfonamides. This statement is confirmed by the numerous examples of dermatitis which follow frequently in the wake of self-medication with patented and/or popular remedies and the misconception that there are specifics for the superficial mycoses.

Immunologic Relationship of Penicillin and Trichophytin. Rostenberg (1946), Peck, and Siegal (1947) have shown that approximately 5 to 6 per cent of adults when given penicillin therapeutically for the first time develop an eruption with a rather characteristic pattern. Evidence of the reaction may

be noted (approximately eight to seventy-two hours) after the drug has been administered. This response is manifest by the rather abrupt appearance of an acute vesicular eruption of the hands and/or the feet including the interdigital surfaces. In addition the groin and other major folds of the body may similarly be the site of an acute eczematous dermatitis often with vesiculation. Regression of this eczematous eruption takes place usually without therapeutic assistance, if the drug is discontinued. The more marked reactions require antieczematous topical medications.

A positive intracutaneous (trichophytin-tuberculin type of response) reaction to penicillin was observed in twenty-four to forty-eight hours when these persons were tested. This form of "silent" sensitivity to penicillin was not found by Peck and Siegal in children under 12 years of age. Men are more commonly affected than women. This form of sensitivity to penicillin may occur without trichophytin sensitivity, though the former is more common. The antigen of penicillin is distinct from that of trichophytin, as indicated by the result of penicillin desensitization experiments, by the close relationship of both antigenic and antibiotic activity of penicillin, and by the distinct chemical and other properties of penicillin and trichophytin. They have suggested that the "silent" sensitization to penicillin develops as a result of epidermal sensitization by penicillin elaborated by fungi. Unlike trichophytin and tuberculin, penicillin sensitization may be possible by multiple injections of penicillin without adequate sensitizing exposure to the fungus penicillium.

Status of Specific Desensitization With Trichophytin.—Immunologic therapy and prophylaxis with trichophytin are, at present, of little practical value in the management of superficial tinea of the skin. Such desensitization is infrequently accompanied by marked or permanent beneficial effects on the majority of chronic or recurrent eczematous and dyshidrosiform eruptions of the hands and feet.

In 1932 Wise and Sulzberger demonstrated that repeated injections of trichophytin made most hypersensitive persons tolerate the intracutaneous injection of many multiples of the dose previously sufficient to produce severe forty-eight hour tuberculin type responses. Some cases of hand and foot eruption of presumptive trichophyton etiology disappeared during the course of the trichophytin injections. These observations have raised hopes for achieving adequate immunologic treatment and prophylaxis in superficial eczematous dermatophytids. The observation that trichophytin injections will regularly and specifically desensitize or hyposensitize the skin to trichophytin has been repeatedly confirmed by other observers.

No one knows why trichophytin hyposensitization as it has been practiced has been disappointing. One may theorize that the extracts employed do not contain all the allergens of the microorganism. The reduction of sensitivity is often transient, is never complete but one of degree, and the reduction of sensitivity has proved to have occurred at certain sites, namely, the sites of injection of trichophytin and need not necessarily be achieved in the affected areas (Wise and Sulzberger, 1937).

Those who work with the perplexing problem of recurrent vesicular eruptions of the hands and feet appreciate the fact that an etiologic diagnosis is extremely difficult. Since neither microscopic nor cultural fungus findings, nor trichophytin tests, nor any other known method can establish the dermatophytid nature of a given case with scientific certainty, it becomes impossible to know how many of the cases of involvement of the hands are actually based on hypersensitivity to trichophytin and oidiumyein and impossible to determine just

what proportion are eczematous eruptions from internal or external sources.

The failure of immunologic therapy in certain eczematous eruptions of the hands and feet may not be due entirely to immunologic inadequacy of present methods. Many of the routine cases of so-called dermatophytoses and dermatophytids are not essentially fungus eruptions, but are examples of eczematous contact dermatitis or external irritants or perhaps foods and, therefore, are not actually based on a trichophylin hypersensitivity. It is obvious that trichophylin desensitization cannot be expected to achieve specific therapeutic effects in such instances.

Formulary

Wet dressings.—The following are useful solutions to employ as wet dressings.

1. Boric acid 2 to 4 per cent (saturated solution).
2. Liq. aluminii acetici N. F. (use as 1:10 to 1:20 dil.).
3. Liq. aluminii subacetici 1:15 to 1:30 dil.
4. Potassium permanganate 1:1,000 to 1:10,000 dil. (must be freshly prepared).
5. Silver nitrate $\frac{1}{8}$ to $\frac{1}{4}$ per cent (useful especially in infected eczematous and mycotic eruptions).
6. Resorein $\frac{1}{4}$ to 4 per cent (useful in secondarily infected mycotic eczema).
7. Tyrothricin Intraderm (Wallace) (useful in infected mycotic eruptions. Dil. 1 to 3 with water).
8. Almay Tar Bath. One tablespoon to large basin for foot bath.
9. Calgon. Dil. $\frac{1}{2}$ to 1 teaspoon to 2 qts. water for wet dressings or foot bath.

Lotions and Emulsions.—

1. Calomine Lotion, N. F. VI.
2. Zinc oxide

Talc	āā 15. to 20.
Glycerin	10.
Aq. dest.	80.
3. Sodium biborate

Starch	10.
Zinc oxide	āā 15.
Lime water	
Rose water	āā q.s. ad 240.
4. Bismuth subnitrate

Zinc oxide	4.
Lime water	8.
Olive oil	āā q.s. ad 240.
5. Calomine Liniment

Lotions should be applied with a small varnish brush. It is sometimes very acceptable to the patient to alternate a drying lotion with an oily one.

Pastes.—

1. Zinc oxide paste, N. F. VI
2. Zinc oxide

Starch	āā 20. to 25.
Aquaphor	q.s. to 100.

The following antipruritics may be added alone or in combination to the lotions or pastes:

- | | |
|------------------------|---|
| Menthol | $\frac{1}{8}$ to $\frac{1}{4}$ per cent |
| Phenol | $\frac{1}{4}$ to 1 per cent |
| Spirits of Camphor | 1 to 3 per cent |
| Liq. carbon. detergens | 3 to 10 per cent |

The following antibacterial, antiparasitic and antieczematous medications may be added alone or in combination to the above lotions and pastes and to ointments and creams:

- | | |
|----------------------|------------------|
| Cinnabar | 1 to 3 per cent |
| White ammon. mercury | 1 to 5 per cent |
| Sulfur | 3 to 10 per cent |
| Icthyol | 5 to 20 per cent |

Vioform	3 to 5 per cent
Resorcin	2 to 6 per cent
Naftalan	3 to 10 per cent
Oil of cade	3 to 15 per cent
Oil of Cadeberry	3 to 15 per cent
Bismuth subgallate	3 to 10 per cent
Crude Coal Tar*	3 to 5 per cent
Salicylic acid*	1 to 10 per cent

Dusting Powders.—

1. Desenex (Wallace and Tierman)
2. Thymol 1 per cent, Boric acid 10 per cent, Zinc oxide 20 per cent, Tale q.s.
3. Vioform (3 per cent) dusting powder
4. Mag. carb.

Ac. boric	āā 8.
Amyli	
Tale	āā q.s. ad 60.

 (with or without 1 per cent Bentonite)

Tinctures.—

1. Salicylic acid 5 to 12 per cent in alcohol
2. Arnings Tincture (modified)

Anthrabin	3 per cent
Tumenol or	
Ichthyol	6 per cent
Glycerin	6 per cent (may be omitted)
Alcohol	
Ether āā	
3. Iodine $\frac{1}{2}$ to 1 per cent in 70 per cent alcohol
Salicylic acid 1 to 2 per cent
4. Gentian violet 1 to 2 per cent (in alcohol or water)
5. Silver nitrate 5 to 10 per cent in water
6. Meta Cresyl Acetate (Cresatin)
7. Castellani's Paint

Basic fuchsin saturated solution	10.
Phenol (5 per cent)	100.
Acid boric	1.
Acetone	5.
Resorcinol	10.

Ointments and Creams.—Infections caused by *T. purpureum* do not respond to the common agents used in the treatment of dermatophytosis. Strong fungicides such as

1. Chrysarobin (fresh) $\frac{1}{2}$ to 10 per cent in petrolatum
or a useful formula suggested by Dreuw.
2. Rectified oil of birch tar 3 to 6 per cent
Chrysarobin (fresh) 2 to 6 per cent
Salicylic acid 2 to 6 per cent
Soft soap
Wool fat āā
3. Dihydroxy-Anthranol (Anthralin) 0.1 to 0.5 per cent

have been found effective. When the hands or feet are involved, the medication is properly applied and worn continuously under a fixed type of dressing for several days (Montgomery, Royal and Casper, 1946). Treatment must be carried out for several weeks to several months to effect a "cure."

Treatment is begun with the lower concentrations, and the strength of the preparation is gradually increased. If dermatitis results, treatment is withdrawn for a few days and soothing ointments applied, after which therapy may be resumed with lower concentrations of the active ingredient.

(*Not used in shake lotions or emulsions.)

The following ointments have been found of service for the healing phase of the eczematous and eczematoid ringworm infections, and for the chronic hyperkeratotic infections other than trichophyton purpureum.

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|--|-----------------------------|
| 1. White ammoniated Mercury | 5-10 per cent in petrolatum |
| 2. Sulfur ppt. | 3-10 per cent |
| Salicylic Acid | 3-5 per cent |
| Lanolin | |
| Vas alba āā | |
| 3. Pragmatar (Smith, Kline, & French) | |
| 4. Desenex (Wallace & Tierman) | |
| 5. Salicylic Acid | 2-6 per cent |
| Benzoic Acid | 3-12 per cent |
| Petrolatum | |
| 6. Iodine Crystals | 2-5 per cent |
| Aquaphor | |
| 7. Quinolol Ointment (Squibb) | |
| 8. Sodium Propionate Ointment (Mycoloid Laboratory, Little Falls, N. J.) | |

For the proper methods of application of topical remedies the readers' attention is called to the excellent presentation *Principles of Topical Medication in Dermatologic Therapy* by Sulzberger and Wolf.

PART X

ENTOMOGENOUS AND PERCUTANEOUS OR DIADERMAL ALLERGY

Mease relates the case of a corpulent farmer who, in July, 1835, was stung upon the temple by a common bee. He walked to a fence a short distance away, thence to his house, 20 yards distant, lay down, and expired in ten minutes. A second case, which occurred in June, 1811, is also mentioned by Mease. A vigorous man was stung in the septum of the nose by a bee. Supported by a friend he walked to his house, a few steps distant, and lay down. He rose immediately to go to the well, stepped a few paces, fell, and expired. It was thirty minutes from the time of the accident to the man's death. A third case is reported by the same author from Kentucky. A man of thirty-five was stung on the right superior palpebrum, and died in twenty minutes.

—GOULD AND PYLE.

CHAPTER LXII

ENTOMOGENOUS ALLERGY

Allergy to insects and their products. When one considers that classical anaphylaxis was first produced by the parenteral administration of foreign protein; that apparently almost any protein may produce the anaphylactic state; and that repeated parenteral administration is a feature of its development, one should not be surprised at the recognition of allergic reaction to the bites of insects. So far the bee, gnat, mosquito and bedbug have been incriminated.

Nor is it surprising to discover that emanations from insects may sensitize by inhalation. In this group we find the mayfly, sandfly (caddis fly), moth, butterfly, flea, bee and the range moth.

In this latter group we should also include allergy to silk, a secretion of the mulberry silk worm, the larva of a small moth, *Bombyx mori*.

Historical.—Cranston Low (1925) reviewed the literature which up to that time indicated the possibility of sensitization to insect bites. Boycott had sensitized two persons, each to a different variety of rat flea, by the simple expedient of allowing the fleas to bite them frequently. While early in the experiment there was no local reaction, following five bites at about weekly intervals, extensive local reaction appeared. Previously unbitten controls showed no such reaction. There appeared to be crossed reaction between the varieties of fleas. Eleven months later the first subject still reacted to one variety but not to the other while the second subject still reacted to both. Stokes has found

that the reactive tissue following the bite of the *Simulium* fly, a variety of gnat, contains numerous eosinophiles. Clewes had had a patient living near Lake Erie in whom a gnat bite caused such swelling as to keep her in bed for several days. Clewes collected the gnats, making a therapeutic extract thereof. After several treatments the lady found that she could lie out near the lake and "be bitten with pleasure." Low also described a Scottish lady who in Norway reacted to mosquito bites, with such edema that the entire face was swollen, the eyes closed and the arms were swollen to nearly double their normal size. The previous year she had been badly bitten by mosquitoes while in Canada with very little consequent discomfort. He believes that sensitization occurred at that time. Other instances collected from the literature by Low are less suggestive of actual allergy. He mentions toxic symptoms following repeated bites with *pediculus corporis*, with associated morbilliform eruption, which disappeared when the lice were no longer fed experimentally on the human subject and which reappeared following renewed feedings. He observes that natives do not react to the bite of the black fly or *Simulium* fly and that white persons in countries where these flies are numerous react rather violently early during their stay, but not after two or three years. He suggests that this may be due to desensitization following repeated bites. It is said that the Indians of South America react very little to the bites of mosquitoes which cause extreme discomfort to white explorers. Pipes* finds the same true of the "cajan fishermen" living in the mosquito-infested bayous of Louisiana.

Percutaneous Exposure

Low mentions the stings of bees, wasps, etc., as being in a rather different category, the reaction being complicated by the injection of a very irritating fluid and the fact that everyone experiences pain and reaction on the first sting. However he mentions, as a possibility, that collapse or even death following one sting from a bee may be due to anaphylaxis. He also directs attention to the fact that those who work with bees and have been stung repeatedly become much more tolerant of stings than others. He distinguishes between biting insects and stinging insects. "From the fact that fleas do not cause a skin reaction after the first bite, that a reaction develops later after repeated bites, that bites from insects show an eosinophilia, and that repeated bites can lead to an immunity, I think we are safe to assume that, unlike the nettle sting, such reactions are sensitization phenomena. Whether reactions from stinging insects are associated with sensitization is not so clear. They may be usually due to irritant poisons, but occasionally to sensitization."†

Allergy to bees.—Benson and Semenov (1930) described asthma in a bee keeper due to sensitization to the sting and to the body dust of the bee. Relief followed hyposensitization with extracts of these two elements.

Asthmatic or anaphylactic reactions from bee sting have been reported by a number of observers including Waterhouse, Goss, Mantous, Hubert, Gibb, Vander Veer, Benson and Semenov. Ellis and Ahrens reported two cases of sensitization to bee protein, in contrast to bee sting. Sensitization was so pronounced that atmospheric exposure was sufficient. One had an attack of asthma after riding in a car containing a robe which had been used a short time previously to wrap a hive of bees for transportation.

*Pipes, David M., Shreveport, La. Personal communication.

†Low, R. Cranston, *Anaphylaxis and Sensitization, with Special Reference to the Skin and Its Diseases*, New York, 1925, Wm. Wood & Co.

They reacted to saline extracts of the head and thorax of the bee. This eliminated the sting which is on the abdomen. They reacted to honey and pollen (chiefly goldenrod) from the hive but not to other goldenrod pollen. After the hive pollen had been washed they no longer reacted. They reacted to secretions from the bee, including the venom. They did not react to bee wings but did to other portions of the body. Saline extract of bee substance which had been subjected to tryptic digestion failed to react. This would indicate that the antigenic substance is protein.

Satisfactory desensitization was accomplished in one case by injections of saline extract of bee substance beginning with a concentration of 1:500,000 and increasing to 1 cc. of 1:50. Five months after discontinuing treatment this patient tolerated daily contact with bees, with no asthma.

Fisher has reported the case of a woman who was stung about fifteen times in 1927 with only normal reaction. In 1928, however, stings were followed by urticaria, later by asthma and finally by anaphylactic shock. Even the handling of an old hat which had not been used for months but which contained many bees' stingers produced asthma.

Desensitization was started with extract of whole bee, the first concentration being 0.00001 mg. nitrogen per cc. The top dose, following weekly injections was 1 cc. of 0.01 mg. per cc. dilution. This dose was then continued at monthly intervals. After full desensitization the patient was stung by a bee. She developed a reaction about 6 inches in diameter and had slight asthma which subsided without treatment.

Vaughan and Pipes have reported the following series of bee sting reactions from the experience of seventy-five doctors scattered through the United States but not previously reported in the literature.

Two young school girls, sisters, were stung, each by a single bee. Both reacted with intense asthma, cyanosis, and collapse. One had general urticaria. Adrenalin relieved both.

A woman was stung by a single bee while standing in her back door. She collapsed before she could reach the dining room. When seen by the physician she was in shock and pulseless. Relief was obtained following adrenalin injections. This patient had had two similar experiences.

A man was bitten by a single bee. He collapsed in the yard. When the doctor reached him he had generalized edema with edema of the glottis. This was before the days of adrenalin, and the patient remained critically ill for several hours.

Two deaths were described, one from the sting of a honey bee and the other from a wasp. No details were given.

Duke (1927) describes sudden death in a child following the sting of a wasp. Bray quotes Miller (1909) as describing asthma and angioneurotic edema from a wasp sting. Arntzen (1934) has described four cases with severe reaction from a single wasp sting, two of them fatal.

I am indebted to Dr. W. A. Plecker, Registrar of Vital Statistics for Virginia, and Dr. O. K. Burnette, Culpepper, Virginia, for description of the following case which may have been a death from bee sting anaphylaxis.

A white man aged 36 had been stung by a yellow jacket bee two years previously, at which time he had severe shock with coma for nearly two days. One year later he had again been stung and collapsed but soon revived. On the occasion of his fatal reaction he was stung by two yellow jackets, one sting on the ankle and the other on the wrist. The physician found no evidence of sting on the arm. On the ankle there was a minute hemorrhagic area close to a vein, with no neighboring edema. The patient promptly went into shock with coma. He died within an hour. It is worthy of note that the bees' nest was investigated and found to contain unusually large bees.

The bee sting reactions described above are different from the following, in which death appears to have been due to the virus although there was evidence of simultaneous allergy, in the appearance of urticaria. The patient was bitten on one arm by eighteen to twenty bees. Hives quickly developed which were relieved within thirty minutes after adrenalin administration. However, the patient continued in collapse and died after forty-eight hours. At autopsy there was a generalized edema in the distribution of the right axillary artery and the right vertebral artery, and extending down the back.

Bedbugs.—Sternberg (1929) discussed a man who had had asthma for twelve years, seasonally, from the second week of July until the end of September. Pollen skin reactions were negative, as were those to other common allergens. He experienced trouble only when at home and when lying on his own bed. Sleeping out of doors relieved him. His bed was found infested with *cimex lectularius*. When similarly exposed out of doors he experienced asthma. The patient reacted strongly to extract of the insects. Specificity was established by positive passive transfer and negative tests on sixty control cases with inhalant allergy. Removal of the cause resulted in relief.

This case should probably be classified as inhalant rather than percutaneous. Churchill (1930), however, described immediate wheal type reactions following bedbug bites, which responded to adrenalin administration.

Mosquito bites. Benson (1936) described four cases of extreme reaction to mosquito bites, in whom testing with mosquito extract produced positive skin reactions, particularly of the delayed type, which did not appear in control cases. Three of the four were relieved following hyposensitization. He found that positive reactions were observed not only to the female mosquito but also to extract of the male. The male does not secrete venom. Extracts of the larva were negative. From this he concluded that allergy occurred to mosquito protein rather than to the venom alone.

The excitant could be extracted in simple saline or buffered saline solutions. Concentrates, made by precipitation of aqueous or saline extracts by cold alcohol and subsequent purification, were more potent. He tested with both the alcohol precipitate and the alcohol soluble extract. The patient who did not respond to hyposensitization with the precipitate was the only one who did give a positive reaction to the alcohol soluble extract. Benson suggests that she may have been allergic to the venom as well as the mosquito protein.*

Flea bite.—The early observations of Boycott have been mentioned. Bray describes the case of a child who reacts with urticaria following flea bites, the wheals occurring not only at the site of bites but also remote therefrom. He mentions a similar case described by Richet.

Inhalant Exposure

One should bear in mind that insects causing allergy following percutaneous exposure may occasionally be responsible also for inhalant allergy. An example is the bee sensitization described by Ellis and Ahrens. However those insects described below customarily cause symptoms following inhalation of their emanations.

Mayfly.—Figley (1929) describes four asthmatics with positive skin reactions to extract of the entire mayfly, one of whom was relieved by hyposensitization. Numerous controls were negative. The mayfly lives but twenty-four hours. During this time it is extremely abundant in those territories

*Brown et al. have described necrotizing lesions from mosquito bites, an Arthus phenomenon reaction.

where it exists. Figley states that it is not unusual along the southern shores of Lake Erie to observe dead mayflies which have been blown against window screens and screen doors making a pile two or more inches deep. The pellicle, which is shed as the fly passes out of the subimago stage, is broken up and carried considerable distances on the wind.

Caddis fly (sand fly).—Parlato in the same year (1929) described similar experiences with the caddis fly which is especially abundant around Buffalo at the eastern end of Lake Erie. It is prevalent throughout the Great Lakes region, and is found less frequently elsewhere. This fly ranks high as food for fresh water fish. The Federal Government assists in its propagation and distribution whenever it seeks to replenish the fish supply of any body of fresh water. Fishermen use the caddis fly for bait.

Allergy to this insect appears to be clear cut, demonstrable by skin test, conjunctival reaction and by passive transfer. An aqueous extract of the whole fly is used for this purpose. Parlato prefers intracutaneous diagnosis using graded solutions, beginning with a solution containing 0.001 mg. nitrogen per cc. and running up to one containing 0.1 mg.



Fig. 258.—Moth scales and hairs in situ on the wing.

The frequency with which he finds positive reactions to this insect in Buffalo gives some idea of its possible importance elsewhere. Five per cent of 850 allergic patients tested routinely reacted to caddis fly allergen. It was found the principal or sole excitant in about one-half of those who reacted positively.

Desensitization appears to be satisfactory, 72 per cent receiving over 90 per cent relief; 22 per cent from 70 to 90 per cent relief, and only 6 per cent receiving less than 70 per cent relief. Preseasonal treatment appears more advantageous than coseasonal treatment. All of nine treated preseasonally obtained 90 per cent relief or better. Eleven of 20 treated coseasonally obtained similar results, while an additional 7 obtained from 70 to 90 per cent and only two obtained less than 70 per cent relief. The total number treated preseasonally is small and it may be that a large number would show some variation from these figures.

Although Parlato has felt that the antigen of caddis fly is a single one and that it is probably related to, if not identical with, that of moths and butterflies, Osgood, by passive transfer and antibody exhaustion experiments, concludes that

two species of caddis fly. *Macronema zebra* and *Hydropsyche chlorotica* *sen alternans* have slightly different antigenic capacities. The latter contains two antigens, the former one. One antigen is common to both species while the *Hydropsyche* contains another in addition.

Caddis fly is of ancient lineage, specimens having been found in the amber deposits of East Prussia whose age is estimated as 45 million years.

The house fly (*Musca domestica*). Jamieson (1938) describes a patient with rhinorrhea and asthma developing when flies buzzed around her face. Positive skin, conjunctival and nasal contact reactions were obtained to the material of the flies' wings. Positive passive transfer was observed. Controls were negative. This patient was also allergic to Russian pigweed, sage, house dust, sweet potato, and cocoa.



Fig. 259.—Detail of moth and butterfly scales and hairs.

Aphiochaeta agarici. Kern (1938) has reported asthma due to sensitization to the mushroom fly in a mushroom culturist. This is a very small black fly scarcely 2 mm. long which inhabits manure. The patient experienced seasonal asthma for a few days each year at the time when the mushroom beds were fertilized.

Tanytarsus. Weil* (1938) states that a tiny insect appears in the late spring and summer on common privet and Japanese privet. Their dead bodies form a white scale on the under surface of the leaves. The insects are small enough to readily pass through a window screen. When resting against a dark background they resemble cigarette ashes. When abundant they form a white cloud if the bushes are disturbed and often accumulate around bright lights. He observed one case of seasonal hay fever with asthma and urticaria giving positive skin reactions to an extract of the insects and relieved by hyposensitization.

*Weil, Clarence K., Montgomery, Ala. In the International Correspondence Club of Allergy.

Moths and butterflies. Parlato has also demonstrated allergy to the emanations of moths and butterflies. The caddis fly is closely related to the moth, resembling the common clothes moth in size and shape. Caddis flies, moths and butterflies are the only insects which shed hairy scales. Parlato presents evidence of crossed sensitization and believes that a person allergic to any of these three will react to an extract of any one. The hairs and scales of moths and butterflies are often seen on pollen slides and may actually far outnumber the pollens in abundance. According to Balyeat, Stemen and Taft the scales appear on slides in June and July in Oklahoma at about the time of the grass season and are far more numerous than the grass pollen grains.*

The New Mexico range moth.—Caffrey is quoted by Randolph as reporting in 1915 that continued contact with the eggs and larvae of the New Mexico range moth produced a tendency to violent attacks of coughing and wheezing, that coryza appeared in many workers and that, after handling the eggs and larvae for several seasons, urticarial reactions appeared, becoming progressively more pronounced.

Randolph's report is of an entomologist who developed asthma after two years' work with the range moth caterpillar. Vasomotor rhinitis had begun much earlier, shortly after he began his moth studies. The patient worked in a poorly ventilated laboratory in which the moth, egg, larvae and a parasite fly were housed. He was found strongly reactive to dust from the laboratory floor and from the floor of the incubation cages, mildly to the eggs themselves, and nonreactive to the fly or to moth wings. He was allergic to the larvae and the eggs. Intracutaneous hyposensitization gave adequate relief. It is especially interesting that the patient also reacted to extract of caddis fly. Controls failed to react to extract of range moth larvae except for one person who had been working under similar conditions for the preceding two years.

Allergy to Silk

The history of silk culture.—The culture of silk probably originated in China although some ascribe it to India. According to Chinese history silk culture was well established a century before the date assigned to the Biblical deluge. The silkworm was domesticated about 2,600 B.C. when the wife of Emperor Hoang-ti first began feeding the caterpillars. The length of domestication is indicated by the fact that the silk moth (*Bombyx mori*) has lost the power of flight, although it still has wings. Moths of other caterpillars which produce various grades of silk, but which have not been completely domesticated, are capable of sustained flight. The Chinese kept the secret of silk manufacture for many centuries. It was not until A.D. 552 that two monks who had lived some time in China smuggled silkworm eggs in a hollow bamboo to Constantinople where, under the protection of the Emperor Justinian, they inaugurated the silk industry in Europe. Byzantium, Greece, Syria, North Africa, Spain, Portugal, Sicily, France and Italy have been in turn the centers of the silk industry in Europe. Belgium and Holland have produced silk for centuries. Today it is an important industry in southern Europe, especially southern France, Italy and Greece. In France, sericulture has had many vicissitudes. The Edict of Nantes was a severe blow since it exiled about 400,000 Huguenots, most of whom were silk workers and many of whom went to England where they attempted to establish the industry. France, however, succeeded in reestablishing her prestige which she again lost with the French Revolution. In the latter half of the nineteenth century disease among silkworms threatened their extinction. The famous investigations of Pasteur demonstrated its infectious origin and the need for most careful sanitation in raising the caterpillars.

* Insects may be collected with the aid of a lamp surrounded by low voltage live wires which promptly kill them. There are several kinds on the market. One is "Electracido," Lewis and Conger, 45th Street and Sixth Avenue, New York. Another is "The Insect Death Ray," A. E. Rittenhouse Company, Honeoye Falls, N. Y.

There have been repeated attempts to introduce sericulture into the United States. Even today it is being carried out on a small scale in California. The chief difficulty has not been failure of the silkworm to adapt itself to this environment but the need for painstaking attention and cheaper labor than is available in this country.

Early colonists imported both worms and mulberry trees. At the opening of the seventeenth century colonial legislatures along the south Atlantic Coast passed an act requiring that ten mulberry trees be planted on every hundred acres. There was a fine for failure to do this and a premium for every pound of silk produced. By the middle of the century interest had ceased. During the last years of the century skilled Huguenots settling in South Carolina were reasonably successful for a number of years, but interest again died out.

The silkworm feeds by preference on the leaf of the white mulberry, also native of China. When the industry was introduced into Constantinople in the sixth century the leaves of the black mulberry, native of Europe and Persia were used. The silkworm does not thrive as well on this although it does reasonably well, but the plant grows too slowly. Much later the white mulberry was imported into Europe. Both it and its cousin the paper mulberry were introduced into the American Colonies during the early attempts at sericulture. Other mulberry trees used are the Japanese mulberry and Alpine mulberry. The osage orange, a



Fig. 260.—Moth scales and hairs in situ along wing margins.

member of the mulberry family, is occasionally used as a substitute but produces an inferior grade of silk. The caterpillars also thrive on the leaves of lettuce and some other plants. Although the silkworm industry died out in the United States, the paper mulberry remains, to shed annually rather large amounts of an extremely toxic pollen, responsible for severe hay fever in those localities in which it was originally planted and also in the lower third of the Mississippi drainage area. Fortunately only a small proportion of the population becomes allergic to mulberry pollen.

Other worms besides *Bombyx* produce silk. Most of these feed on oak leaves and do not produce beautiful white silk. It cannot be satisfactorily bleached. Pongee and shantung silks are derived from such sources. There are native silkworms of North and South America which have never been commercially exploited or cultivated. They feed on a much larger variety of food including the leaves of oak, apple, maple, hickory, willow, sycamore, etc.

Sericulture.—The silk moth lays its eggs on sheets of paper which are kept in a cool place until after the mulberry trees have sprouted leaves. The eggs are then placed in the sun or in an incubator, to hatch. The larval worms commence to eat the leaves at once and grow rapidly. Within two months they molt four times, shedding the skin each time. During this interval they eat several thousand times their original weight of leaves. After the fourth

molting the caterpillar reaches its full length, about three inches. During growth two large sacs or vessels have been forming along the sides of the body in which a sticky fluid is stored. The openings to these sacs, called spinnerets or seripositors, are located in the lower lip. When it is about to spin, the so-called caterpillar ceases to eat. A tiny stream of sticky fluid issues from each spinneret. If the fluid is forced from the body it hardens at once. But, manipulated by the silkworm, it is drawn out as it hardens into a beautiful strand of silk. Strands from the two sacs are joined together to form one thread. This is woven by the worm into its cocoon, by a continuous rotary motion of the head. Completion of the cocoon requires three days, occasionally slightly longer.

The regular motion of the head results in the spinning of a continuous thread which can be quite easily unwound and which may be from 2,000 to 3,000 feet long. The completed cocoon is about one and one-half inches long, egg shaped.

The chrysalid remains in its chrysalis for from two to three weeks, when the mature moth emerges. The moth averages about one-half inch in length. The male is slightly smaller than the female. They eat little or nothing. The females lay 500 or more eggs, then die. The males do not survive them long. Their lives as moths last but a few days. The females cannot fly, while the males can steady themselves in defense but cannot fly upward.



Fig. 261.—A row of ancient mulberry trees at Williamsburg, Va., imported by the early settlers in an effort to establish a silkworm industry.

Treatment of the cocoon.—A number of the finer specimens are selected for breeding. The remainder of the cocoons are used for silk. The chrysalid is killed by dry heat or boiling to prevent its further development and cutting of the silk thread. The cocoon is then softened in warm water which dissolves the gum that binds the silk fibers together. The outer strands which are not continuous are lightly brushed off and the brushing is continued until the loose end of the long fiber is caught. It is then gradually unwound, twisted with other similar strands and reeled. The cocoons remain in the water during this process.

Formerly the outer and inner layers with broken threads were discarded along with double or imperfect cocoons and those from which the moth had emerged by cutting through the thread. Such silk was called silk waste. Today these short fibers are spun into silk thread in much the same way that cotton is spun. We therefore have spun silk and reeled silk.

Before dyeing, the sticky gum is entirely removed from the silk by boiling in soapy water. Such silk does not have the beautiful sheen of finished silk which has been treated with dyestuffs and metallic salts to give it weight and luster. Some of the cheaper grades of silk still retain the natural gum which gives it a certain amount of body and finish.

Nature of the silk allergen. Although Clarke and Meyer (1923) reported a case of asthma due to silk which they attributed to the gum or glue adherent to the silk fiber, and Figley and Parkhurst (1933) likewise expressed a belief that the gum or glue in the raw silk serves as an allergenic agent, Parlato and Swarthout believe, from studies made with the different portions of the cocoon and the silkworm itself, that it is the latter that provides the excitant.

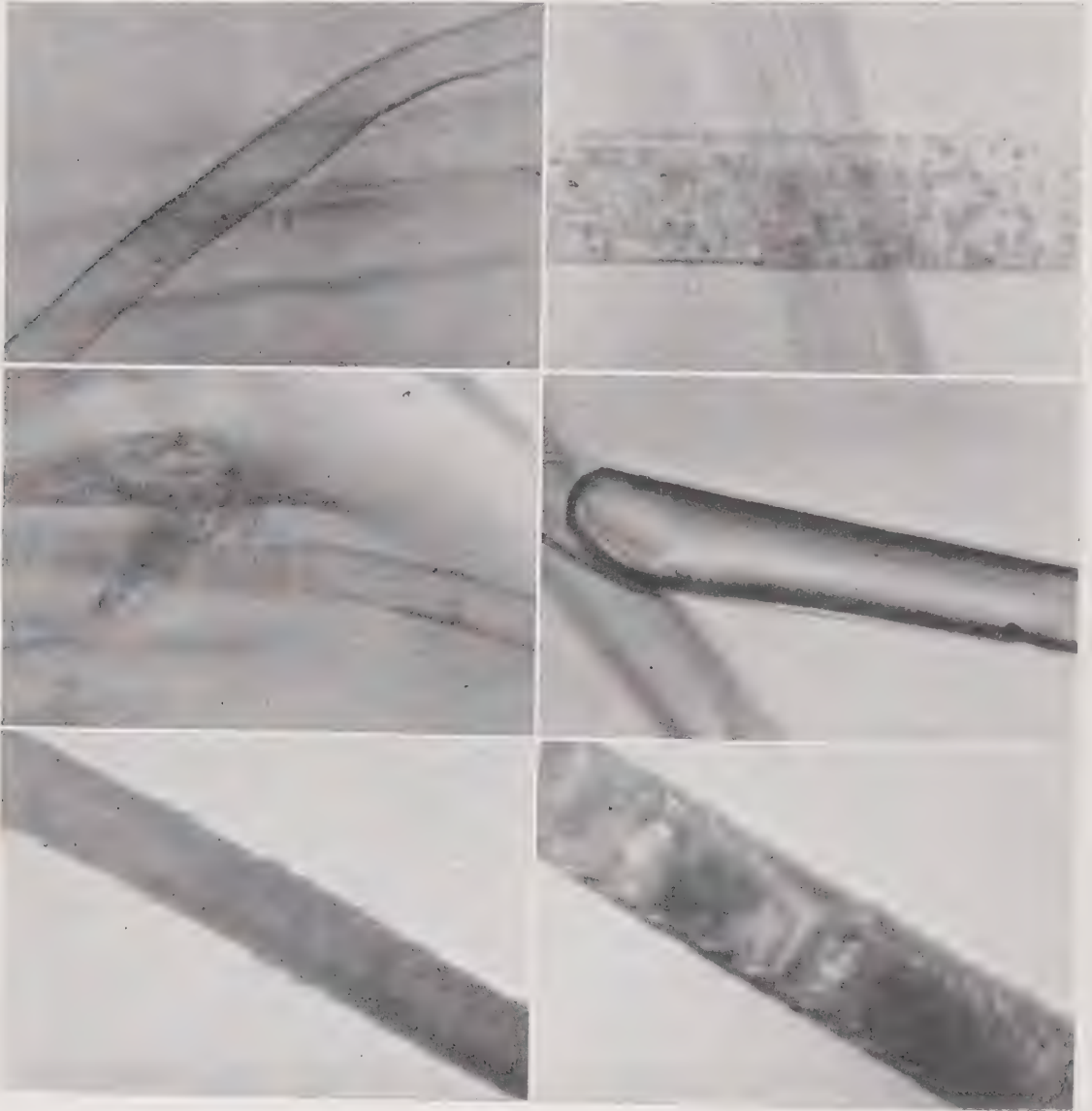


Fig. 262.—Fibers and hairs. These may sometimes be differentiated by microscopic study. Top left, silk; top right, rayon; center left, linen; center right, kapok; bottom left, wool; bottom right, dog hair.

There are three possible sources of the allergen: the silk fiber itself; its gum or glue, termed "sericin," utilized in the making of the cocoon; and the pupa or silkworm itself. Parlato and Swarthout confirmed the earlier work of Milford (1931), who states that the pupa contains at least ten times as much allergen as the cocoon.

Although we must accept these observations and grant that in all probability the allergen is more abundant in the worm itself, the fact remains that in

view of undoubted sensitization to silk cloth, which contains no pupa and relatively little sericin, some of the excitant must persist in finished silk.

Obviously extracts should not be prepared from finished silk but from crude silk from which the sericin or glue has not been removed, or from the worm. It would be interesting to know whether positive reactions occur also to the mature moth and whether there is any evidence of crossed reaction between the silk moth and other moths and butterflies.

Extracts may be made in the usual manner, with buffered saline or one of the glycerin extracts, with standardization by weight, by volume, total nitrogen or protein nitrogen content.

Clinical manifestations.—Allergy to silk localizes most often in the skin, either as an urticaria, atopic dermatitis or, less often, contact dermatitis. At times it is responsible for inhalant symptoms, asthma and allergic coryza. There is a tendency toward nonspecific positive reactions and the writer finds that, to be of significance a positive silk reaction must be rather strongly so. Walzer states that passive transfer may be positive especially in eczema and that when so, the positive reaction is of significance. His customary intracutaneous testing strength is of from 0.001 to 0.01 mg. nitrogen per cc.

The major portion of so-called contact dermatitis due to silk has been found due to some other constituent of the cloth such as the dye. Silk is more likely to cause atopic dermatitis than contact dermatitis, presumably due to inhalation of the excitant. For example a patient with disseminated atopic dermatitis had severe exacerbation whenever she wore silk dresses. Even silk stockings caused some symptoms, but not on the legs, which were in direct contact.

Atopy vs. contact allergy.—Although dermatologists as a group have been slow to apply the allergic hypothesis to the study of skin diseases, within the last few years the contact test has stimulated more general interest among them. Many still feel that the older method of scratch and intracutaneous testing is of little value in dermatology, but more recent developments, as illustrated in the study of silk allergy, show the importance of these methods to this field of medicine.

This applies especially in atopic eczema or neurodermatitis. As early as 1844 Cazenave reported that flare-ups of neurodermatitis tended to alternate with certain visceral manifestations, among which he listed gastralgia, neuroses, neuralgia, recurrent bronchitis and asthma.

Neurodermatitis is an unfortunate name and indeed its originator, Brocq, later substituted the term, "pruritus with lichenification," as preferable. More recently the term "atopic dermatitis" has come into favor as distinguishing neurodermatitis from contact dermatitis or eczema. The basic objective difference between the two is that neurodermatitis appears to first involve the lower layers of the skin and is not associated with vesiculation, while contact dermatitis appears to involve the superficial layers and is often accompanied by vesiculation and weeping.

In atopic eczema or neurodermatitis the distribution is usually rather characteristic, certain skin areas being favored, particularly the antecubital fossae, the popliteal spaces, the neck and face, sometimes extending down on to the chest and back. In contact dermatitis the favored areas are usually the exposed areas, face, neck, hands and ankles. Other areas sometimes involved are usually explained by certain habitual occupational contacts.

In neurodermatitis the first symptom is usually itching and this is later followed by deep pseudopapule formation. Scratching becomes a prominent symptom and as the condition becomes chronic, lichenification results, with thickening and induration, but as a rule without vesiculation. Variability or fluctuation is usually prominent and this is especially true of the degree of pruritus.

The importance of silk allergy as a cause of neurodermatitis has been clearly brought out by the studies of Figley and Parkhurst, Taub and Zakon, and of Sulzberger and Vaughan. These studies have also demonstrated quite conclusively the reason for failure of positive contact reactions in neurodermatitis and have explained the mechanism by which the skin lesion becomes manifest.

While the patient with contact dermatitis usually gives a positive patch reaction, the victim of neurodermatitis customarily fails to react positively to patch test, even when he is allergic to what appears to be a contact substance such as silk. It is the patient with atopic dermatitis who gives the positive scratch or intracutaneous test. Figley and Parkhurst first emphasized this in silk allergy, expressing their belief that the skin manifestation was due, not to contact, but to inhalation of the silk allergen with consequent blood stream distribution to the shock tissues in the skin. They reported five cases of neurodermatitis clearly allergic to silk by scratch and endermal tests but negative by contact. They emphasized the widespread distribution of silk particularly as an inhalant allergen. Silk becomes well distributed into house dust from draperies, upholstery, rugs and clothing.

Taub and Zakon reported three cases of atopic dermatitis associated with silk sensitization, again with positive scratch or endermal reactions or positive to passive transfer, but with negative patch reactions. They carried the investigation a step farther by blowing powdered silk protein into the nostril of a silk allergic. Within a few minutes marked itching was complained of, followed by violent sneezing and a watery nasal discharge. Repetition with two other silk allergies produced pronounced pruritus of the skin.

Sulzberger and Vaughan next studied a woman with disseminated neurodermatitis, extremely reactive to silk. Her serum was introduced into the skin of nonallergic recipients. Passive transfer was demonstrated by a positive reaction to silk in the passively sensitized skin. The passively sensitized individuals then inhaled 50 mg. amounts of dry powdered silk antigen. The passively sensitized areas reacted after about 20 minutes with urticaria, thereby demonstrating that the silk inhaled through the nose of a nonallergic was carried in the blood to the passively sensitized sites in the skin.

Feder passively sensitized himself to silk. He then tested the sensitized area with silk antigen obtaining a low-grade positive wheal. The following day he put on a fresh pair of silk socks. An hour later the wheal flared up again.*

Incidence.—Although there is considerable difference of opinion as to the frequency with which silk sensitization plays a part in allergy, it seems probable that this is a relatively frequent offender. The two reports which give it highest percentage are those of Balyeat who found skin tests positive in 9.9 per cent of a series of 181 cases of atopic dermatitis and of Sulzberger who found positive silk reaction in nearly all of a series of atopic dermatitis. Taub and Zakon feel that it is less important as an allergenic factor.

*Feder, J. M., Anderson, S. C.: Personal communication.

Intensity of reaction.—On one point there seems to be fairly general agreement. Persons allergic to silk are apt to react severely to extremely high dilutions. The writer has seen a mild constitutional reaction with flare-up of generalized dermatitis from a scratch test with 1:500,000 concentration. Because of this and similar experiences we never start hyposensitization with a concentration greater than 1:50,000, often one much more dilute.

Treatment.—Treatment must be commenced with extremely high dilution from ten to a hundred times higher than that for other inhalant allergens. Toxic symptoms from overdosage may occur even in high dilution. Where indicated, hyposensitization may well be attempted although improvement is usually only partial and the results are not altogether satisfactory.

CHAPTER LXIII

SERUM DISEASE

This was the first allergic disease recognized as such. It is not surprising in view of the following facts: (a) it was a new disease, appearing at about the same time that anaphylaxis was first being studied; (b) it followed the parenteral administration of foreign proteins, a procedure similar to that in experimental use; (c) the sequence of events was comparable to that observed in laboratory animals; (d) biochemical changes, especially in the blood, were soon found to be similar in the two conditions. Even today, serum disease in its three major manifestations more closely resembles experimental anaphylaxis than do any of the other clinical allergies. There are points of difference which, however, do not invalidate the assumption of an identical basis.

Probably the first description of a clinical reaction to the intravenous administration of a foreign serum was that of Dallera (1874) who described urticaria appearing ten days after transfusion with lamb's blood. Similar cases as well as more explosive ones were observed promptly after the introduction of diphtheria antitoxin and it was thought for a time that the antitoxin itself was in some way responsible. However, as early as 1895 Bertin in France and Johannessén in Germany showed that the same symptoms could be produced with normal horse serum, containing no antitoxin. The disease was first clearly described and interpreted by Von Pirquet and Schick in their monograph which appeared in 1905.

Incidence.—Daut (1897) stated that the frequency of serum reactions depended upon the amount of serum used. Pirquet and Shick (1905) reached a similar conclusion, and stated that over 85 per cent developed serum sickness if the amount of serum used were as much as 100 to 200 ml. Coca (1928) stated that 90 per cent of persons would show reactions provided a sufficiently large dose of serum were used. Hunt (1932) reported a series of two thousand eight hundred fifty-nine individuals who had received purified and concentrated serum, and found that the number reacting did not differ materially from the figures obtained in earlier years with unrefined and unconcentrated serum. Stimson (1940) agreed that the greater number of reactions occurred when large quantities of serum were used, and that it was the amount rather than any refinement of serum which determined whether reactions would occur.

Types of serum disease.—They clearly describe the delayed reaction, known today as serum sickness, the accelerated reaction which may follow reinjection of serum, and the immediate reaction known today as anaphylactic shock or constitutional reaction, which may follow reinjection or may occur after the first injection in a person atopic to horse serum.

Although the normal incubation period of serum sickness is from eight to twelve days, Von Pirquet and Schick observed that when second injections were given after an interval of four months or more, the symptoms of serum sickness were accelerated, appearing as early as the fifth day or even sooner. If the second injection was given at an interval of less than four months, the reaction might be accelerated or immediate, within a few minutes or a few hours.

Serum sickness. Today we recognize these three phases as episodes in the development of serum sensitization. A person not allergic to horse serum may, following a first injection, become so after the usual interval of about ten days. It has been shown that horse serum continues to circulate as such in the patient's blood until the advent of serum sickness, when precipitin and other evidences of antibody formation usually appear, following which the horse serum as such rather rapidly disappears and the serum sickness terminates. This may be interpreted as evidence of beginning sensitization, symptoms appearing because antigen is still present. It has been shown that serum sickness is more likely to develop following the introduction of larger amounts of serum. With small quantities sensitization may develop but serum sickness itself is much less frequent.

Immediate reaction.—The immediate or explosive reaction which may occur on reinjection after the usual incubation period and up to an interval of about four months, is the prototype of anaphylactic shock in a sensitized animal. It may occur in one who has received large or small amounts of the first or sensitizing dose and therefore in one who may or may not have experienced serum sickness.

Accelerated reaction.—The accelerated reaction follows reinjection after a longer interval. The time of onset and the severity of symptoms vary, depending on the diminution in the intensity of sensitization, with the lapse of time. Very early accelerated reactions may merge into the immediate type, while the long delayed ones are indistinguishable from ordinary serum sickness. We may say, therefore, that the time of onset of serum disease following reinjection is a rough measure of the persistence of sensitization following an earlier injection. Such artificial sensitization has been shown to be still present as long as seven and one-half years following the first injection.

Serum atopy. Such serum reactions in originally nonsensitized persons are to be distinguished from reactions of an entirely similar character which occur, fortunately very rarely, in persons naturally sensitized to horse serum or horse dander. As we shall see, while the mechanisms of the two are probably identical, there are certain points of difference which are of considerable practical importance. The serum of the "natural" horse asthmatic is more likely to contain reagin, demonstrable by passive transfer, and may, therefore, be properly spoken of as naturally atopic (Coca). Such an individual is sensitized to horse dander as well as serum. Desensitization is usually much more difficult, indeed, usually impossible, due either to the much higher grade of sensitization, or to the manner of reaction to the atopen, or possibly, as suggested by Coca, to a fundamental difference in the nature of the sensitization.

Definitions. Although some writers speak of the reaction which follows the incubation period after a first injection as "serum disease," it seems to the writer more appropriate to apply this to all of the reactions, and to call the former "serum sickness." This term is now widely used with this connotation. With this slight change in terminology the writer therefore adopts Mackenzie's definitions, as follows:

Serum sickness is "an allergic reaction resulting from the parenteral administration of a foreign serum and characterized by an incubation period, skin eruption, enlarged lymph nodes, fever, edema and polyarthritis."

Serum accidents are "immediate, shock-like, sometimes fatal reactions which occur in individuals who are hypersensitive to the serum administered." These may occur in naturally sensitized individuals following first injection or in others following a second injection given within a relatively short time after termination of the incubation period. A serum accident is probably identical with constitutional reaction or anaphylactic shock as occasionally observed after the administration of other atopens.

Accelerated serum sickness may occur after considerably less than the usual incubation period. It follows second injection rather than first injection and appears to be associated with more rapid formation and accumulation of antibodies, this being in turn dependent upon the previous similar "experience" on the part of the reactive tissues.

Symptomatology

Serum sickness.—The customary incubation period is from eight to twelve days, although it may be shortened, especially if serum has been given at some time in the past. The longest recorded interval following injection is 26 days. Any of the following symptoms or any combination thereof may constitute the disease.

Fever occurs customarily at the onset, preceding the eruption and disappearing before the latter subsides. It is usually irregular, lasting from seven to ten days, sometimes with subsequent recrudescences. The *eruption* is the most constant symptom. It may take any of three general forms, (a) *urticarial*, (b) *morbilliform*, sometimes resembling erythema multiforme, or (c) *scarlatiniform*. The last so closely resembles the eruption of scarlet fever that the two may be clinically indistinguishable. The absence of the characteristic picture in the tongue and throat and the absence of subsequent desquamation helps to differentiate them. In the measles-like eruption, the absence of Koplik's spots is of significance. Itching may be intense, especially in the urticarial form. Often the eruption commences at the site of injection, especially if the latter was subcutaneous or intramuscular, preceding the general eruption by hours or by a day or two.

Lymphadenopathy, like the eruption, is a frequent symptom. It usually commences prior to the latter, and never results in suppuration. Only the regional glands near the injection site may be involved or there may be a generalized enlargement of the superficial nodes. The spleen may also become palpable.

Joint symptoms appear as a polyarthritis, usually after onset of the eruption, and involving chiefly the more distal joints of the extremities, except the phalangeal joints which are not usually involved. Polyarthritis is more likely to be a symptom after the injection of large amounts of serum. According to Walzer it never enters the picture of the atopic constitutional reaction. The frequency of joint manifestation is given by Bray as from 1 to 2 per cent of all individuals injected and by Sturtevant as 14.3 per cent of patients with serum disease. Symptoms range from slight pain and stiffness to swelling, redness and severe pain, scarcely distinguishable from the picture of acute rheumatic fever. Boots and Swift find that aspirated joint fluid contains about 20,000 cells per cubic millimeter, with 60 to 70 per cent polymorphonuclear leukocytes, and shreds of fibrin. It was not distinguishable from similar fluids obtained from the inflamed joints of rheumatic fever. Precipitation tests with this fluid show the presence of horse serum.

Edema and urinary changes sometimes suggest an acute nephritis. Edema is said to occur in about one-third of cases and involves especially the face and ankles. Albumin and casts may appear in the urine. When the two occur together a differential point from acute nephritis is that the edema antecedes the urinary changes.

Gastrointestinal symptoms are not frequent. They include abdominal pain, nausea, vomiting and diarrhea which may be bloody.

Tachycardia and general prostration are frequent.

Neurologic manifestations may be cerebral, radicular, neuritic, or polyneuritic. Longcope has described transient hemiplegia attributed to meningeal edema. Root pains and evidence of peripheral neuritis, especially of the brachial plexus, may complicate the picture. The latter are more frequent after tetanus antitoxin. Peripheral neuritic symptoms may appear as late as two or three weeks after the commencement of serum sickness. Foster Kennedy has described permanent damage to the brachial plexus and paralysis of the long thoracic nerves, attributed to local edema of the neural tissue. He also describes one case with fulminating cerebral symptoms, hemiplegia, hemianopia, aphasia, etc., attributed to a similar reaction in the meninges.

Hematologic changes are not striking. The onset may be preceded by slight leukocytosis. Throughout the disease there is usually a leukopenia with relative lymphocytosis. With subsidence of symptoms 3 to 7 per cent eosinophilia has been observed.

Serum sickness occasionally takes on a *recurrent form*. As many as four recurrences at short intervals have been described following a single serum injection. The skin manifestations, in any of the three forms above described, are the most constant features of recurrent serum sickness. The phenomenon has been attributed to the development of sensitization after varying intervals, to different constituents of the blood serum. Coca points out that recurrent serum sickness occurs only after the administration of whole serum, not when the pseudoglobulin fraction alone has been injected.

Hooker observed a curious intracutaneous skin reaction following the injection of whole horse serum, with three distinct responses occurring at intervals of several hours. He isolated the proteins from this horse serum, injecting them separately into the same individual's skin. Reaction followed each, after intervals varying by more than twenty minutes. This suggests sensitization to three different excitants in the serum.

Mackenzie states that recurrences may occur after free intervals of from 4 to 14 days. He, also, suggests that the relapse may represent reaction to different portions of the complex antigen. Dale and Hartley have shown that antibodies appear earlier against serum albumin than against serum globulin.

Uncomplicated serum sickness is never fatal.

Shock reactions or serum accidents. These present the picture of constitutional reaction, described elsewhere. They may occur at once, almost before the needle is removed, or may be delayed as long as thirty minutes, rarely more than an hour. They may occur at any interval after one hour but are rarely as severe as the immediate reaction. Death has followed the administration of one drop of serum intravenously (Boughton, 1930). Symptoms may involve special tissues such as the skin, nose or bronchi, but the more acute the reaction, the more it presents the picture of general shock without

localized manifestations. Tuft remarks on the constant presence of dyspnea without asthmatic breathing on auscultation. This is corroborative of Waldbott's insistence that pulmonary edema rather than asthma is the characteristic response in allergic shock.

If the patient with constitutional reaction commences with wheezing, sneezing or urticaria, the probability of recovery is much greater than if he suddenly turns ashen, cries out in apprehension and appears to suffocate.

Factors in the Acquisition of Serum Allergy

Omitting for the present discussion natural horse atopy, what are the factors which in some measure control the acquisition of sensitization? Which factors may be controlled in some degree, to prevent the phenomenon? The literature on this subject is voluminous. For greater clarity the writer presents merely the consensus arrived at by a number of investigators.

1. One may become allergic, reacting to a second injection, even though one did not experience serum sickness following the first injection. However, those who do develop serum sickness after first injection are more likely to have symptoms following subsequent injections.

2. Children from allergic families are more likely to become sensitized than those of families in which no allergy exists.

3. Plain horse serum is less likely to produce sensitization (8 per cent) than serum mixed with toxin (50 to 75 per cent).

4. Site of introduction plays a part. Constitutional reactions occur most frequently following intravenous injection, less so after intraspinal, and still less following subcutaneous or intramuscular administration.

5. The development of sensitization as manifested by serum sickness depends also upon the amount injected. About 10 per cent of those receiving less than 10 cc. become sensitized, as contrasted with 90 per cent of those receiving 100 cc. or more. About 32 per cent of those receiving from 20 to 60 cc. become sensitized.

Mackenzie found that among 16 patients who had received from 100 to 1,000 cc. of serum, 2 to 8 years previously, skin reactions were positive in 87 per cent. There was no correlation of the degree of skin reactivity with the severity of previous serum disease, the amount of serum given, or the time interval prior to skin testing.

6. Although the incidence of serum sickness depends upon route of administration and the volume of serum, there is evidence that very small doses are capable of sensitizing, especially when combined with toxin. The amount of serum in a dose of diphtheria toxin-antitoxin is about 0.0001 cc.

Following the observation by Hooker (1924) that toxin-antitoxin administration tended to sensitize to horse serum, there has been considerable study of the subject. Some of the conclusions are rather contradictory. Hooker found that 27 per cent of cases so treated subsequently developed positive skin tests to horse serum.

Park (1924) and Bauer and Wilmer (1926) concluded that toxin-antitoxin does not promote horse serum sensitization. Spicer reached similar conclusions in 1928.

On the other hand, Crooks (1924), Stewart (1926), Lathrop (1927), and Gatewood and Baldrige (1927) reported untoward reactions which they at-

tributed to previous administration of toxin-antitoxin. In 1929 Gordon and Creswell reported a survey of a large series of serum injections. Of 556 patients who had previously received toxin-antitoxin, 74 per cent gave serum reactions. Of 151 who had had no previous toxin-antitoxin and who received therapeutic serum, there were 43 per cent reactions. This latter series had received therapeutic serum previously but no toxin-antitoxin. In 1750 who had never received any previous serum or toxin-antitoxin only 16 per cent manifested serum reactions.

The work of Hooker in particular has given rise to the impression that toxin increases the tendency to become sensitized to a particular substance when the two are administered together. This is the basis of Burkey's recent work on *Staphylococcus aureus* toxin to which we have referred elsewhere.

Tuft has found in a study of 100 children that the injection of diphtheria toxin-antitoxin sensitizes 27.9 per cent of children to horse serum. Sensitization is manifested by positive skin tests and by passive transfer, indicating that tissues of the body other than the skin are also sensitized. The tendency to acquire this sensitization was influenced by the personal or family allergic predisposition. Allergic children appear to become more easily sensitized.

Other evidence indicating the possibility of sensitization with extremely small quantities of plain serum, not combined with toxin, is the observation of Jones and Mote and of Simon and Rackemann, who sensitized humans to rabbit protein and guinea pig serum by repeated intracutaneous inoculations.

7. Among other factors which control in a measure the tendency toward serum sensitization are the manner of preparation, the nature of the organism against which the horse has been immunized and the horse itself. In the discussion of recurrent serum sickness we have seen that purified or concentrated serum, consisting chiefly of the globulin which contains the antibody, is less likely to cause serum sickness than whole serum. Sensitization, as indicated by serum sickness, is less likely to occur with sera from horses immunized against streptococcus and pneumococcus than against tetanus or diphtheria toxins.

Park has observed that sera from certain horses cause more serum sickness than those of others and that skin test sera from different horses vary in efficacy. Positive reactions in a series of individuals were observed in 10 per cent, 35 per cent and 60 per cent respectively, with sera obtained from three different horses.

8. Age plays some part. Both Rackemann and Tuft, among others, remark on the greater tendency of children to develop serum sickness. Coca states, however, that the incidence of serum disease is quite the same throughout life.

9. Race also plays a part. Coca found serum sickness less frequent and less severe in the American Indian than in the Caucasian.

Fatal Reactions

Although death in an immediate serum accident or other allergic shock is fortunately rare, it is more catastrophic for the relatives and the doctor, not to mention the patient himself, than any other potential misadventure in the treatment of disease. The embarrassing feature of anaphylactic death from serum or following the injection of any other allergen is that, theoretically at

least, it could have been prevented. At the same time there is some consolation to be derived from Jungeblut's statement that "the total incidence is distinctly below the recorded fatalities from general anesthesia or salvarsan therapy."

Clinically the immediate reaction is the same whether it be in an artificially sensitized person or in a natural horse asthmatic. We shall discuss both forms.

Park concluded from the study of 350,000 serum injections that one out of 50,000 may be followed by a fatal reaction and one in 20,000 by alarming symptoms. These were usually not intravenous injections. Bullowa† estimates an average of one anaphylactic shock with or without death in every 700 intravenous injections of horse serum.

Lamson found in the literature from 1893 to 1929 only 44 cases of fatal anaphylaxis. Of the 18 in which autopsy was performed 13 died after first serum injection. In 8 there was a history of previous serum injection. It should be noted, therefore, that fatal anaphylaxis may occur not only in natural horse atopies but also in acquired serum allergy. Some emphasis has been placed on the fact that desensitization prior to serum treatment is difficult, almost impossible with natural allergies. However, shock or death may occur in both forms of serum allergy. Deaths have followed reinjection of serum but Gillette (1909) stated that almost all cases of sudden death from diphtheria antitoxin followed the first injection. It certainly is true that deaths do occur following the first injection and no patient should be given serum without careful consideration of the possibility of reaction.

Kojis (1942) studied a series of 6,211 cases receiving horse serum and found five deaths or a rate of 1 in 1,042, which is a much higher figure than those previously given. Forty-one patients had reactions within an hour after injection. If the skin test was positive the chances of serum sickness was increased four times, immediate reactions 35 times, and the mortality, 11 times. With positive conjunctival test, serum sickness was five times and immediate reactions 173 times more frequent than if test were negative. Secondary injections increased serum sickness by 50 per cent, and immediate reactions were 23 times as often. Intramuscular injections increased the immediate reactions by 14 times, and intravenous injection increased them 62 times. These figures represented diphtheria antitoxin injections.

Other fatalities have been reported (Sheppe, Burgess, Tuft, Bullowa and Jacobi) since the summary by Lamson. Nevertheless, the incidence of alarming reactions and fatalities is undoubtedly much higher than one would judge from the literature. With this in mind Vaughan and Pipes questioned 75 physicians, not allergists, from various parts of the United States concerning their own experiences with alarming or fatal serum reactions. The replies included not only their own experience but the experience of others in their neighborhood concerning which they had authentic information. The following reports were received from this small number.

A patient was being tested intracutaneously with 0.01 cc. of undiluted horse serum prior to antitoxin administration. He died in five minutes. There had been no previous scratch test.

*Jungeblut, Claus W., in *Agents of Disease and Host Resistance*, edited by Frederick I. Gay, Charles C. Thomas, Springfield, Ill., 1935.

†Bullowa, Dr. Jesse, New York. Personal communication.

A death was reported from plain horse serum given subcutaneously for postpartum hemorrhage. Allergic history and the history of possible previous serum administration were not obtained.

A case of severe shock from an intracutaneous test with mule dander extract was recorded.

A negro boy with diphtheria was given antitoxin. He had had no previous serum injection. Within three minutes he went into collapse. He was given adrenalin and recovered. Four days later he had serum sickness.

Antipneumococcus serum intravenously resulted in coma with slow pulse. This occurred very soon after injection and may have been psychic.

A boy who had had tetanus antitoxin two years previously was given another prophylactic injection without preliminary skin testing. He went into shock but recovered.

A patient was being tested with tetanus antitoxin, 0.1 cc. of 1:10 dilution being given endermally. Before the syringe could be cleaned the patient reacted with nausea, vomiting, sneezing, asthma and urticaria. Treatment with adrenalin resulted in prompt relief within thirty minutes.

The cook in a certain family had diphtheria. The father, a physician, decided to immunize his two daughters who were twins. One of them had had hives and he hesitated to give her serum. To the other, who had no allergic history, he gave 1,000 units of diphtheria antitoxin. She died in five minutes.

In another family a child had diphtheria. The family physician decided to immunize the entire family. The father dropped dead shortly after receiving his injection.

A patient who had had a previous serum injection was given scarlet fever antitoxin. Within five minutes he was in collapse and pulseless. He was given adrenalin and recovered, but later died from scarlet fever.

A patient with scarlet fever, no allergic history and no history of previous serum injection, was tested endermally with erysipelas streptococcus antitoxin. The reaction was negative and the patient was therefore given 2 cc. of antitoxin intravenously over a period of ten minutes. One hour later he had severe reaction with cyanosis, dyspnea, thready pulse, no urticaria. Relief followed adrenalin injections.

Tetanus antitoxin was given prophylactically to an injured man, the injection being into the abdominal muscles. One minute later he developed angioneurotic edema of the face with wheezing and said that he could not get his breath. Adrenalin gave relief. Six days later he had regular serum sickness. This man had had eczema as a baby and had had toxin-antitoxin three years previously.

In addition there were brief mention without details of an immediate death following diphtheria antitoxin; a death from serum, type unknown; and one near death from diphtheria antitoxin, given some time after toxin-antitoxin mixture had been given.

Obviously, if this is representative of similar groups of physicians in the United States, serum reaction is by no means rare. Certain it is that adequate precautions should always be taken to establish the absence of allergy prior to serum administration. These steps will be discussed later.

The most recent case report is that of Freedman which we quote in some detail since it illustrates so well the occurrence of an immediate reaction when the reinjection is given at the optimal time for maximal sensitization.

Freedman reports the death of a 6-year-old boy following intracutaneous testing with horse serum. For years the boy had had recurrent attacks of asthma and eczema. Twenty days before his fatal catastrophe he had received an injection of diphtheria toxin-antitoxin which had been followed after 6 days by a severe attack of asthma. This lasted several days and on the third day of asthma urticaria became a prominent symptom, presumably due to serum sickness. The child was given 0.05 cc. of horse serum intracutaneously as a test for sensitization. Two minutes later a large wheal formed at the site of injection, followed by generalized urticaria. A minute later the child doubled up, complaining of severe abdominal pain. In a few seconds he stopped breathing and could not be resuscitated. He had received over 1 cc. of adrenalin before respiration ceased.

Necropsy findings.—Fatal cases of anaphylactic shock have shown pathologic findings similar to those of experimental anaphylaxis. Some have shown hepatic and splanchnic engorgement resembling anaphylactic shock in

dogs; others show pulmonary distention and emphysema similar to the picture in guinea pigs; while still others have presented the picture of right heart failure similar to that observed in the anaphylactic rabbit.

Prevention of Serum Sensitization

Obviously, if one must give foreign serum, there is no way in which to prevent possible sensitization or the consequent development of serum sickness. However, serum sickness occurring at the end of the usual incubation period following a first injection is never fatal, although it may be most uncomfortable and inconveniencing. Indirectly it may occasionally be responsible for a fatal outcome when one is suffering from some other much more serious malady such as pneumonia, septicemia, severe scarlet fever, when the added burden of the serum reaction may be sufficient to determine a fatal outcome.

Since immune sera have been found efficacious in the prophylaxis or treatment of an increasing number of diseases, there is a growing tendency toward specific serotherapy. With it there is often an increased tendency toward its careless use, in cases where the indication is not clear-cut or urgent.

Obviously, prophylactic injections should not be given except when definitely indicated. Reinjection should be avoided, especially within the first three or four months following the first injection. Intravenous injection should not be employed if another method will serve as well. Purified or concentrated sera should be used by preference. The advent of prophylactic toxoid, especially for diphtheria and tetanus, is especially welcome since it involves no serum administration in the prophylactic procedure.

The Detection of Serum Sensitization

Two groups of individuals may be reactive, the atopics who have become allergic, usually to horse dander, and who as a rule give a history of horse asthma or allergic coryza, and those who have received previous serum treatment. In certain areas of Europe where horse meat is eaten by the poor and in parts of Russia where mare's milk is fed to children, there is a third group who have become allergic following alimentary absorption.

Anamnesis.—Obviously the interrogation of the patient should bring out any history of asthma or other allergic disease whether due to horses or not; history of allergy in the family; record of any previous therapeutic injection, whether with horse serum, or serum (antitoxin) combined with toxin; history of serum sickness; and a record of the time elapsed since any previous serum injection.

As has been brought out above in the description of the twin girls, immediate reaction may occur in a person with no history of previous injection or horse sensitization or even of allergy, but is more likely to occur with those in which there is a family history of allergy. Sutliff reported that only 16 per cent of his patients with immediate symptoms gave histories indicative of previous sensitization of any sort.

Therefore, although one should proceed with special care in the presence of a suggestive history, one should not accept a negative history as an adequate safeguard, but should carry out preliminary tests prior to any serum

injection. Even then, one cannot be entirely sure. Sutliff found that serum skin tests were sometimes negative in persons who experienced reactions, and, conversely, positive in some who did not. In spite of the lack of entire reliability, skin testing should be performed.

Preliminary tests.—The majority of writers suggest preliminary skin tests with horse serum diluted 1:10. Some suggest 1:100 dilution. Some recommend 0.05 cc. endermally, others 0.01 to 0.02 cc. The smaller amount is always preferable, giving as much information as the larger, and avoiding the reaction to the greater trauma which might be misinterpreted as a low-grade positive reaction.

Serum should be diluted, not only as a precaution against constitutional reaction but also because many normal persons react, with some erythema, to undiluted serum, thus confusing interpretation. It is probable that 1:100 dilution is sufficient to avoid a fatal reaction even with the most highly allergic. As a preliminary test 1:10 endermally is, in the writer's opinion, too near the margin of safety to be recommended.

Program.—The following diagnostic schedule is therefore recommended. Preliminary scratch test should be made with 1:10 dilution of serum. This is roughly one hundred times less reactive than the same concentration endermally. If preferred, one may substitute a preliminary endermal test, 1:100, or 1:1000. If after twenty or thirty minutes the scratch reaction remains negative, a conjunctival test is done with the same 1:10 dilution in physiologic saline. The delicacy of this lies between that of the scratch and the endermal reactions. It may be read at the end of five to eight minutes following which, if negative, an endermal test is performed with the same 1:10 dilution. If this last test is positive, it will be so within ten or twenty, rarely as long as thirty minutes. In actual practice the time can be materially shortened with an overlapping of the tests and their readings. The scratch test is read after fifteen minutes. If negative, the conjunctival test is applied but the scratch test is watched for another ten or fifteen minutes. If the conjunctival reaction is negative at the end of five minutes the endermal test may be started, actually within twenty minutes from the time the scratch test was begun. The desired information is therefore obtained within thirty to forty minutes. This may appear to be an unnecessarily complicated procedure when the results are negative for the first one thousand times but here, probably more than in any other phase of allergy, it is the duty of the allergist first and foremost to protect his patient against a very generally recognized potential cause of unnecessary death.

A final diagnostic step, possibly unnecessary but one which gives the operator a greater sense of security when administering serum, is to give the first therapeutic 0.02 cc. undiluted, intracutaneously. This he will watch during the first ten minutes or more of treatment or, better, while completing preparations for commencing treatment. The reaction remaining negative, one may proceed with greater confidence.

It is probably better to use normal horse serum for testing rather than the therapeutic serum which is to be used. Foshay has observed that individuals infected with tularemia show an immediate edematous-erythematous reaction to antitularense horse serum and goat serum. They give a negative reaction to normal horse or goat serum. Such an immediate reaction might

be misinterpreted as positive. In this event serum therapy, clearly indicated, might be withheld. At the present this may be considered demonstrated only for antitularemia serum. However it should be borne in mind as a possibility with other immune sera.

The conjunctival reaction is usually considered less nonspecific than the skin test, that is, giving fewer false positive and false negative reactions. As pointed out by Tuft, it is not reliable in children in whom the act of crying may produce an unusual redness, or tears may wash away the test substance. Since an unusually severe reaction might cause some degree of corneal damage, it is well to wash away the test substance as soon as an indubitable positive has been recognized, using 1:1000 adrenalin or a mixture containing 4 cc. of 1:1000 adrenalin and 12 cc. of saturated boric acid solution.

Prevention of Serum Accidents

There are certain disease states in which the indications for antitoxin or immune serum are so definite that one would be guilty of negligence were one to avoid its use merely because of fear of an untoward reaction. In other conditions, especially those in which serum therapy has not yet demonstrated unquestioned superiority, one would often be justified in withholding this treatment, especially if the preliminary studies described above show evidence of sensitization.

Occasionally a person ill with a disease such as diphtheria or tetanus, who undoubtedly needs the protection of serum therapy, is found sensitized to horse serum. In this case desensitization should be attempted but it should not be carried to the point of endangering the patient's life. In these maladies the medical profession has been taught the need for early serum treatment and there is an urge to get the material into the patient as rapidly as possible. It is far better, however, to risk the hazard of further inroads of the infection during the slower process of desensitization than the other horn of the dilemma represented by the hazard of anaphylactic shock.

Sera other than equine.—If a person urgently in need of serum therapy reacts to horse serum, it should be borne in mind that therapeutic bovine, goat and sheep sera are available for some conditions. In general, such sera are to be preferred to desensitization. One of these may be substituted after preliminary tests for possible sensitization. Larger quantities are required since these sera do not usually contain as much antibody as does horse serum.

In the presence of sensitization, purified, concentrated sera are to be preferred.

The question of primary atopic sensitization.—We must digress at this point to discuss the problem of those naturally allergic persons, spontaneously sensitized to horse emanation. Investigators with wide experience in this field state that rapid desensitization is impossible and horse serum should not be given under any circumstance, no matter how carefully. Its careful administration might cause no harm, but it will be impossible to increase the dose to such a stage as to be therapeutically effective. Wherein lies the difference between the naturally atopic and the person who has become sensitized from previous serum administration?

The horse asthmatic is primarily allergic to horse epithelium, horse dander. He is usually also sensitized to horse serum, although such a person, sensitized to dander, is occasionally found who does not react to horse serum. According to Coca (see below) such a person may be given horse serum. Duke has described a man who could not go near horses but tolerated three subcutaneous injections of horse serum without ill effect.

Ratner and his associates, likewise Forster, have demonstrated that horse dander and horse serum contain a common antigen. The horse serum antigen is present in only very small amounts in dander; in large quantities in the serum. Dander contains at least one other antigen and this latter is not present in serum. Horse asthmatics, allergic to both antigens, will react to horse serum. Those sensitized only to the dander antigen will not react to the serum. These observations have been confirmed by Tuft.

Forster reached his conclusions with a study of the precipitin test, Ratner with the anaphylactic test and Tuft with the neutralization test. Evidence of two allergens therefore appears to be conclusive. Tuft has described a series of horse asthmatics who received horse serum without untoward effect and concludes that it is advisable to test all allergic patients to horse serum both by skin and eye test before dismissing them as unsuitable subjects for serum administration merely because of the existence of an allergic state.

The question arises as to the manner in which the horse asthmatic becomes sensitized. Is he fundamentally different from the artificially sensitized? Is natural atopy to horse serum fundamentally different from horse serum sensitization following a previous injection? Ratner and his associates appear to have answered this question adequately by sensitizing guinea pigs through inhalation of horse dander and subsequently shocking them with intravenous horse serum. An analogous situation in humans would explain apparently primary sensitization as being actually secondary, due to previous inhalation and absorption of the allergen.

Cooke (1947) does not agree. He states that this sensitization probably is not induced by horse dander for "from the guinea pig experiments on anaphylaxis there is no proved antigenic relationship between the two antigens."

However, most observers believe that there is no basic difference between those primarily and secondarily allergic to serum. The difference appears to lie in the intensity of the sensitization and in the fact that such persons are also allergic to other horse allergens. Tuft concludes from his studies that natural or atopic sensitization is basically the same as the acquired anaphylactic type in serum disease.

This being the case, there is no contraindication to attempting desensitization in both types, but with a realization that it is difficult, especially dangerous and sometimes entirely unsatisfactory in horse asthmatics who react to serum as well as to dander.

General principles.—In view of the probable failure of desensitization of horse asthmatics who react to horse serum, the following general rules laid down by Coca* are subscribed to by the author.

*Coca, Arthur F., in *Asthma and Hay Fever in Theory and Practice*, Charles C. Thomas, Springfield, Ill., 1931.

"1. If the patient is known to be the subject of asthma due to horse dander and if the ophthalmic and cutaneous tests with a 1:100 dilution of horse serum result positively, the injection of therapeutic horse serum is contraindicated.

TABLE LXII.—COCA'S RULES FOR SERUM THERAPY

PARAGRAPH IN TEXT	HISTORY OF HORSE ASTHMA	ENDERMAL TEST	CONJUNCTIVAL TEST	PASSIVE TRANSFER	PROCEDURE
1	+	+	+	-	Don't treat
2	+	0	0	-	Give cautiously
3	0	+	+	-	Don't treat
4	0	+	+	0	Give cautiously
5	0	?	0	-	Give cautiously

"2. If atopic hypersensitiveness to horse dander is known to exist in the patient and if, nevertheless, the intracutaneous and ophthalmic tests with horse serum diluted 1:10 result *negatively* it is proper, *so far as is known*, cautiously to administer the therapeutic serum. The patient in these circumstances is sensitive to the dander, but not to the serum.

"3. If both the cutaneous and ophthalmic tests with the diluted horse serum result positively, even in the absence of clinical signs of sensitiveness to horse, this result should contraindicate any attempt to inject the therapeutic horse serum.

"4. However, in such a case where serum is urgently needed, the physician should not give up without making the indirect test (passive transfer with patient's serum in the skin of a substitute), as first recommended by Clarke and Gallagher. In one instance of this kind in a young woman of atopic parentage, but without any personal history of atopic symptoms, both the skin and the eye reacted markedly to a 1:1,000 dilution of horse serum. The result of the indirect tests (carried out in several normal persons) was entirely negative and the patient tolerated a prophylactic dose of tetanus antitoxin, experiencing only a severe urticaria and angioneurotic edema which, however, could be controlled with epinephrine.*

"5. In the absence of clinical evidence of sensitiveness to horse and if the ophthalmic test with 10 per cent horse serum results negatively, an urgently needed injection of horse serum may be administered without an intracutaneous test because in these circumstances a positive cutaneous reaction would not indicate a constitutional hypersensitiveness (Park). This must be true also if the patient has previously received an injection of horse serum (Park).

"Fatalities very rarely follow the intravenous primary injection of therapeutic horse serum into nonatopic persons in whom both ophthalmic and intracutaneous tests with a 1:10 dilution of horse serum resulted negatively. The cause of such deaths is unknown."

Desensitization

In the absence of positive findings as described above, serum may be given without delay. If given intravenously not more than 10 cc. should be given in the first ten minutes. Thereafter it may be introduced somewhat more rapidly.

There is no general standard technic of hyposensitization, although those recommended follow the same general program. That outlined below may be considered overly cautious, but the writer believes that this is a procedure in which caution may be considered one of the major virtues. Furthermore it possesses the advantage that so far as the writer has been able to determine, when used in conjunction with the testing procedure described above, it circumvents by a safe margin the "extremely small dose" fatal episodes reported in the literature. One drop of undiluted serum intravenously has killed. Endermal testing with undiluted serum has killed. There have been serum accidents at the point of change from a properly performed preliminary sub-

*This paragraph added later by Coca (personal communication).

cutaneous desensitization to intravenous injection. The one factor not controlled and which cannot be controlled except by the exercise of reasonable judgment during the procedure is that of cumulative effect following successive injections.

Failure of subcutaneous protection.—Tuft described a case in which 8 cc. of serum had been given subcutaneously over a period of two and one-half hours and yet the patient died following the subsequent very slow intravenous injection of not more than 10 cc. He concluded that insufficient time is often allowed for absorption from subcutaneous injections. He established that from fifteen to twenty-four hours must elapse before the major portion of subcutaneously injected serum is absorbed. It becomes apparent that building up to a much larger dose subcutaneously than is later given intravenously does not assure preliminary systemic exposure to as much serum allergen as may be contained in the first intravenous dose. We should therefore look upon the first subcutaneous desensitizing series as a preliminary trial, rather than as the first phase of desensitization. If serum is to be given intravenously, we should consider the first intravenous injection, following the subcutaneous series, as the first desensitizing dose and should make the initial intravenous dose smaller than any that has ever caused fatality or severe reaction.

Procedure for Hypodermic or Intramuscular Desensitization

Materials needed.

1. Therapeutic serum
2. Sterile physiologic saline of approximately equal volume
3. Three syringes, preferably tuberculin type
4. Epinephrine 1/1000
5. Tourniquet.
6. Two 5 cc. sterile rubber capped vials for mixing serum dilutions, each containing 4.5 cc. of sterile physiologic saline.

In the absence of reaction at any stage during the program, injections are to be given at twenty-minute intervals. Undiluted serum, 0.5 cc., is withdrawn with a tuberculin syringe and introduced into vaccine vial No. 1 containing 4.5 cc. of sterile physiologic saline. This is well shaken, and labeled "1:10 dilution." The syringe is laid aside, to be used later with undiluted serum. For subcutaneous or intramuscular injections of 1:10 dilution, a fresh sterile syringe is employed. "Dilution 1:100" is prepared by transfer of 0.5 cc. from the 1:10 bottle to vial No. 2, containing 4.5 cc. of saline. A fresh syringe is used for this purpose.

Injections of 1:10 serum are given successively in different localities of one arm, in the following schedule.

- | | |
|------------|---------|
| 1st dose : | 0.1 cc. |
| 2nd dose : | 0.2 cc. |
| 3rd dose : | 0.4 cc. |
| 4th dose : | 0.6 cc. |
| 5th dose : | 0.8 cc. |

Twenty minutes after the last injection the same schedule is repeated, with undiluted serum, the first three injections being in the same arm, the

last two in the other arm. A final dose of undiluted serum, 1 cc., is given either in the second arm or on the inner aspect of one thigh. Either syringe may be used for the undiluted serum, being kept, aseptically, between injections or, better, sterilized each time. Injections are given deep, subcutaneously or intramuscularly, not superficially for two reasons. First, one desires rather rapid absorption, as rapid as may be safe; second, there may be considerable local reaction several hours later which is less painful if the injections have been deeper.

Three hours have been needed for this preliminary desensitization. If the entire amount is to be given subcutaneously or intramuscularly, the same process is continued, the dose being doubled each time.

Control of reaction.—Injections having been given into the extremities, systemic absorption in the event of a constitutional reaction may be delayed by the application of one or more tourniquets. Adrenalin 0.5 to 1.0 cc. should be given subcutaneously into the flank or at least into an area not controlled by a tourniquet. The same dose may be repeated as indicated, but one should give the first dose time to achieve its effect before giving the second. Two or three minutes often suffice for the appearance of adrenalin effect (amelioration of symptoms, tremor, tachycardia, nervousness). From this point the control of reactions follows the program described in the discussion of constitutional reaction.

No more serum should be given until all tourniquets have been released for thirty to forty-five minutes without recurrence of shock symptoms. The next dose should then be not more than one-third or one-fourth of the last preceding dose and subsequent increases should be not more than 50 per cent instead of 100 per cent.

Intravenous hyposensitization.—After one has reached a top dose of 1 cc. of undiluted serum in the preliminary subcutaneous therapy, it is safe to start intravenous desensitization with 1:100 dilution. Use a fresh syringe which has not been used with the 1:10 or the undiluted serum. The following doses are given at twenty-minute intervals.

TABLE LXIII.—INTRAVENOUS SCHEDULE AFTER PRELIMINARY SUBCUTANEOUS TREATMENT

DOSE	CONCENTRATION	QUANTITY
1	1/100	0.1 cc.
2	"	0.2 cc.
3	"	0.4 cc.
4	"	0.8 cc.
5	1/10	0.1 cc.
6	"	0.2 cc.
7	"	0.4 cc.
8	"	0.8 cc.
9	Serum, concentrated, or, better, diluted with equal amount of saline	0.1 cc.
10		0.2 cc.
11		0.4 cc.
12		0.8 cc.
13		1.0 cc.
14		2.0 cc.
15		4.0 cc.
16		8.0 cc.

Following this 17 cc., the entire remaining amount may be given.

This program has the disadvantage of the large number of requisite venipunctures, but these may be done entirely satisfactorily with a 26 or 27 gauge needle. There is no need for larger needles, at any rate until the larger quantities of undiluted serum are being given.

An alternative, probably equally safe, more rapid, and less inconveniencing to the patient would be continuous or intermittent veniclysis. The reservoir is first filled with 100 cc. of 1:1000 serum in physiologic saline. At least one hour is allowed for the introduction of this amount which corresponds to 0.1 cc. of undiluted serum. One hundred cc. of 1:100 extract is then introduced into the reservoir and introduced at the same rate, the entire amount corresponding to 1 cc. of undiluted serum. Following this, undiluted serum is introduced with a syringe in the following schedule, the interval between injections being thirty minutes.

0.2 cc.
0.4 cc.
0.8 cc.
1.6 cc.
3.2 cc.
6.4 cc.
12.8 cc.

Thereafter the entire amount may be given. If the serum is diluted with equal quantities of physiologic saline these volumes may be doubled.

Control with epinephrine.—In an extreme emergency epinephrine may be given intravenously. However, 1:1000 concentration produces distressing epinephrine symptoms. Ampules of 1:10,000 adrenalin are available which may be used for this purpose, in 1 cc. doses, repeated if necessary at from three- to five-minute intervals.

Tuft recommends the giving of a small initial dose of adrenalin (0.3 cc.) at the outset of treatment, with repetition at hourly intervals through the course of injections in order to prevent the occurrence of immediate reaction. If signs of serum reaction appear, adrenalin dosage should be stepped up to 0.5 or even 1 cc. if necessary. Adrenalin does not diminish the efficacy of the serum.

Symptoms of reaction.—Except in the presence of fulminating shock, previously described, beginning symptoms are those of systemic reaction. The patient becomes somewhat restless, tends to scratch various parts, may complain of irritation of the nose or actually sneeze. If the condition progresses he usually breaks out with urticaria and develops some degree of asthma. In the presence of a systemic reaction of this sort, wheezing is often heard, in contrast to the absence of this symptom in constitutional reaction.

Causes of fatal serum accidents. Former serum fatalities were unavoidable, due to the unknown nature of the reaction. We have learned much from these accidents. Fatalities today may usually be ascribed to (1) failure to recognize the harmful potentialities; (2) failure to test for sensitization; and (3) unjustified attempts at short cuts in the process of desensitization. The critical period as far as fatal serum accidents are concerned appears usually to have been during the administration of the first 10 cc. and, in highly sensitized patients, the first fractions of a cubic centimeter.

Immunologic Findings in Serum Disease

The close resemblance between serum reaction on reinjection and experimental anaphylaxis has been mentioned. The occurrence of serum sickness, a week or longer after a single injection, a phenomenon not characteristically observed in experimental anaphylaxis, has been attributed to serum still present as such in the system at the time when antibodies have been formed in large quantities. If human serum disease and experimental anaphylaxis are basically the same, one would anticipate a shock type of reaction very regularly after previous serum administration. Instead, serum is usually given a second time without untoward effect. However, it should be borne in mind that antibodies become less active with the lapse of time and that if the second injection were always given early after the incubation period the result would probably be otherwise. Thus, Longcope concludes that if sufficient serum is given in a reinjection at any time between the thirty-fifth and eightieth days following the first injection, an immediate reaction is likely to occur in about 60 per cent.

Precipitin titer.—It has been shown in studies of serum sickness that antigen and antibody as measured by precipitin titer may be present simultaneously in the blood. Precipitins increase markedly at about the time of recovery from serum sickness. The antigen disappears rapidly at about this time. Severe symptoms of serum sickness appear chiefly in those who develop a high precipitin titer. Those who are relatively insusceptible to reaction show little or no precipitin in the blood.

It should be noted parenthetically that although there is evidence that horse serum continues to exist as such in the blood until the time of serum sickness, this does not necessarily apply to all types of antigen. The period of persistence varies with the nature of the protein. We have noted elsewhere that pollen allergen may be found up to 48 hours after injection. Kenton (1938) reports that crystalline egg albumin introduced intravenously into rabbits disappears rapidly; 85 per cent in one hour, 94.4 per cent in two hours and 99.6 per cent in 24 hours.

After a month or more the serum antibody titer gradually diminishes.

However, the time relationship between the appearance and disappearance of symptoms and precipitin is not clear cut, varying rather widely. Furthermore, while atopic antibodies (reagins) responsible for positive transfer reactions, are quite constantly present in horse asthmatics allergic to horse serum, their appearance in acquired serum sickness is evanescent and inconstant. Horse asthmatics are said to show little or no precipitin in the serum. It should be borne in mind that precipitin may be present in the cells, absent in serum, and that this is rather characteristic of atopic allergy.

Heterophil antibody. Finally, there is an entirely different type of antibody, the heterophil antibody which is so markedly increased in serum disease as to be of diagnostic value. Heterophil antibody is the antibody for a non-species-specific antigen discovered in 1911 by Forssman. This investigator injected rabbits with emulsions of guinea pig organs, especially kidney, thereby producing an hemolysin for sheep red cells. Similar reactions may be produced with the tissues of several other animals. Horse serum is one of these, containing heterophil antigen. Human blood contains heterophil antibody after horse serum sensitization. That is, antibodies against sheep

erythrocytes appear, along with horse serum antibodies. Taniguchi (1922) suggested that a reaction between these antibodies and the heterophil antigen in the reinjected horse serum might be the cause of serum sickness. Davidsohn (1929) presented suggestive confirmatory evidence.

However, Powell, Jamieson and Kempf (1935) purified serum (tetanus antitoxin), removing the heterophil antigen. Using this alternately with non-purified serum from the same original batch, they found that the frequency of human serum sickness was the same in both groups. The sensitizing and shocking properties as observed in animals were the same. They conclude that development of serum sickness and development of heterophil antibody in humans are not directly related. The heterophil antigen which may be present in horse antisera does not appear responsible for serum sickness.

In serum sensitization we are therefore faced with the problem of interpreting the significance of three types of reactive bodies, precipitin, heterophil antibody and the skin sensitizing antibody or reagin. None of the three shows a constancy of reaction in serum disease. The bulk of evidence indicates that all manifestations of serum disease have a common basis and that this basis is similar to, if not identical with, that of experimental anaphylaxis. However, none can deny the statement by Coca that there are still many gaps to be filled in before proof or otherwise of an identity can be established.

The Arthus Phenomenon

There is one more clinical manifestation of serum disease which is fortunately rare. Its similarity to the Arthus phenomenon is so striking that its description under this title appears justified.

The blood of sensitized guinea pigs contains very little free antibody as measured by the precipitin test. The blood of sensitized rabbits contains relatively large quantities of precipitin. Arthus (1903) reported that following successive weekly subcutaneous injections of an antigen such as horse serum there gradually developed at the sites of inoculation, first edema, then induration which sometimes proceeded into necrosis and aseptic ulceration. The phenomenon appeared after the third injection. Injections were not made at the same site. It was believed that this reaction, easily obtained in rabbits but not in guinea pigs, was dependent in some way upon the higher precipitin content and probably upon a local combination of precipitin and antigen in the tissues. It has since been shown that local anaphylaxis of the Arthus phenomenon type may occur in any organ of a sensitized animal following direct contact with the antigen. Gastric ulcer has been produced by the injection of antigen into the mucous membrane of sensitized rabbits' stomachs. Lesions have been produced in the kidneys, liver, pericardium, myocardium, brain, lung, testis, joints and peritoneum of sensitized rabbits. Glomerular nephritis has been produced following injection of the antigen into the renal artery.

Opie states that "local anaphylaxis or the Arthus phenomenon is an inflammatory reaction which occurs when an animal immunized against a protein is reinjected with the same antigen; it is caused by an antibody present in the blood stream and tissues of the immunized animal and occurs when antigen and antibody meet in the tissues."

Clinical examples.—When serum is reinjected very shortly after the customary incubation period there may be considerable local reaction at the site

of second inoculation, instead of a more generalized reaction. The local lesion appears as redness, induration with local tenderness and heat, and often pruritus. As a rule this disappears gradually over a period of a day or so and only rarely does it progress to necrosis. This is comparable with the Arthus phenomenon.

Gatewood and Baldrige (1927) described six cases with severe local reaction and necrosis appearing at the site of repeated injections of toxin-antitoxin mixture. This they likened to the Arthus phenomenon. Lesné, Richet Jr. (1913), also Tumpeer (1931, 1933), have reported similar cases. Ross described a fatal case in a child who was given intragluteal scarlet fever streptococcus antitoxin during an attack of serum sickness. The skin manifestations so closely resembled those of scarlet fever that an absolute differentiation could not be made. Lucas and Gay (1909) first described this type of lesion in human beings. They found that the percentage of cases with such reactions increased directly with the number of injections at short intervals after the primary injection.

Shwartzman has listed the reports of human Arthus phenomenon to date as made by Koehler and Heilmann, 1923; Gatewood and Baldrige, 1927; Irish and Reynolds, 1933; Tumpeer, 1933; Ross, 1934; and Maroney, 1934.

In the case of Irish and Reynolds a 28-month-old boy had received diphtheria toxin-antitoxin in a series of three injections seventeen months previously. He was given three intramuscular injections of meningococcus serum on successive days, two in the right buttock and one in the left, for the treatment of a supposed meningitis. Four days later he received another injection into the left buttock. There followed a local blanching of the skin and after an hour, generalized urticaria with edema of the face, fever of 103° and delirium. At the end of an hour the blanched left buttock became purple. The following day a fifth injection was given in the right buttock with similar local reaction. The local discoloration, tenderness and swelling on both buttocks persisted, spreading around toward the abdomen. Fever continued. Seven days after the fourth injection blebs appeared on the buttocks. Two days later the areas became darker and the swelling subsided but four days after this the buttocks turned black and a bloody watery discharge appeared. Gangrene had developed. The child eventually died.

In Meleney's case (1930) a child received a prophylactic dose of scarlet fever serum. Becoming ill with the disease several weeks later, he received a large dose of scarlet fever antitoxin. At the site of second inoculation severe and intensive gangrene developed. In this case it becomes obvious that the Arthus phenomenon type of reaction may occur after longer intervals.

As far as is known at present there is no way in which the rare Arthus phenomenon necrosis may be avoided except through the avoidance whenever possible of repeated subcutaneous administration, especially at frequent intervals, of days or weeks. Treatment is symptomatic.

Homologous Serum Reaction

Theoretically, transfusion with compatible human blood, when properly performed should produce no reaction, more particularly no allergic reaction. Allergic reactions have been encountered following human blood transfusions. These have usually been attributed either to the introduction, with the blood, of the specific allergen to which the recipient was sensitized or to the introduction of blood containing antibodies against an antigen present in the recipient. Both Bray and Tuft have reviewed the literature on this curious phenomenon. They record the following reports.

Antibody or Reagin from Sensitized Donor, Introduced into the Recipient Where It Comes into Contact with Antigen

Ramirez (1919). The donor was sensitized to horse dander. For a time following transfusion the recipient who had not previously been horse allergic could not go near horses without developing asthma.

Berger (1924). The donor was a horse asthmatic. The recipient, with purpura hemorrhagica, had had horse serum and antistreptococcus serum to arrest hemorrhage, without benefit. Thirty-five cc. of donor's blood intramuscularly resulted in generalized urticaria and slight dyspnoea. Horse serum repeated eight days later caused severe urticaria.

Sureau and Polacco (1933). Donor had had injections of "anthesis" for hemorrhage two years previously. Recipient continued to bleed after transfusion and was given an injection of anthesis. A sudden allergic reaction followed. Anthesis, chamomile, is a stomachic to which allergy has been reported by Rowe.

Holder and Diefenboch (1932) reported the case of a woman recipient who, following transfusion, experienced attacks of urticaria following the eating of strawberries. It was then found that the donor had, all of his life, suffered violent urticaria from strawberries.

Antigen present in donor's blood is transfused into a recipient who is sensitized thereto.—

Duke and Stofer (1924). A woman with pernicious anemia was allergic to milk. She received 1000 cc. of blood from one donor. Fifteen minutes later transfusion was started from a second donor who was not allergic to milk but who had taken a considerable quantity just prior to the transfusion. There was an immediate allergic reaction requiring 3 cc. of adrenalin in divided doses for relief.

Duke and Stofer (1924). This was a similar case in which tomato and cabbage were the allergenic excitants.

Sureau and Polacco (1933). A horse allergic with anemia was shocked following transfusion with blood from a donor who had received antitetanus serum.

Vaughan and Pipes (1936) described the case of a recipient who was allergic to egg. The donor ate eggs two hours prior to transfusion. Blood matching had been satisfactory, both direct and by blood groups. The recipient experienced severe dyspnea after receiving 75 cc. of blood. Although he had had eczema in the past he had never had asthma.

These authors record another case with similar development in which the donor, feeling that he was going to be very much depleted after the loss of blood drank a quart of milk just prior to the transfusion.

Possible Transfer of Both Antigen and Antibody

Tedstrom's case experienced generalized urticaria practically immediately after transfusion. The recipient gave no history of allergy. The donor, strongly allergic to strawberries was experiencing hives at the time of transfusion, from eating strawberries. A later transfusion from the same donor at a time when he had not eaten strawberries and was not experiencing urticaria was accepted without allergic reaction.

Prevention

To prevent such incidents both donor and recipient should be questioned concerning allergic sensitizations and possible antecedent serum therapy. Bray suggests the preliminary intravenous injection of small amounts of the donor's blood with a pause to allow for possible reaction, before transfusing the remainder. He also advises that adrenalin be kept available during transfusions. A fasting donor is less likely to transmit possible allergenic foods to the recipient.

Nonspecific Treatment

Epinephrine is the remedy of choice for immediate effect. It may control adequately the symptoms of serum sickness but may have to be repeated frequently. Epinephrine in oil may have more lasting effect. Ephedrine and Propadrine or other analogues may help. Benadryl and Pyribenzamine give excellent relief in a large per cent of cases. They may be repeated as needed over as much time as is required for relief. Fifty or one hundred milligrams may be given to adults with due regard to side reactions that not infrequently occur with the use of these drugs.

PART XI

ANAPHYLACTIC SHOCK

Anaphylactic shock is an experimental curiosity, of high informative value, but not of any obvious significance in determining survival or extinction during the evolutionary progress of a species. The sudden introduction of antigenic substances into the circulating blood is not an event which is likely to menace any living thing, unless it is subject to intentional human interference. It is not really paradoxical or surprising that a mechanism which, in natural circumstances, tends directly towards immunity, should react to the disadvantage of its possessor, when exposed to a stimulus which formed no part of the environment in which it was evolved.

—TOPLEY AND WILSON.

CHAPTER LXIV

ANAPHYLACTIC SHOCK

Frequency.—A review of the literature reveals surprisingly few accounts of clinical anaphylactic shock. Lamson discovered 41 reported cases between 1894 and 1923 in which death may have been due directly or indirectly to protein injections. Thirteen of these followed diphtheria antitoxin; 7 followed injection of other types of serum. There were an additional 21 cases “in which information was lacking or in which death seemed due to primary disease or some other causes not associated with injected substances.”

Vaughan and Pipes reviewed the literature from 1924 to 1936, finding 69 additional cases of severe shock or death. It is interesting that while nearly all of the early cases summarized by Lamson were associated with serum disease, only 52 per cent of the more recent series had experienced shock or death from serum. The second series is summarized in Table LXIV.

It seems that one hears of more cases of severe shock or death than are recorded in the literature, and the impression is gained that these reactions are much more frequent than published communications would indicate. This is understandable since the physician who has experienced such a catastrophe might well prefer to forget it as soon as possible. However, since these regrettable incidents have been the misfortune of leaders in medicine, one should not hesitate to publish his own experience, indeed should do so not only as a matter of record to prevent similar unhappy experiences among others but also as a matter of self protection.

Author's survey.—Feeling that allergic shock and even death are probably more frequent than indicated in the literature, Vaughan and Pipes (1935)

made a survey of physicians' experiences along this line. During the demonstration of an exhibit on allergic shock at the meeting of The American Medical Association, as many as possible of the doctors who stopped at the booth were interviewed concerning any catastrophes that they had had or had known of among their colleagues. This was a random sampling, done during lull periods, and it must be acknowledged that a physician who had had such an unfortunate episode might have been more likely to stop at the exhibit booth.

A total of 50 physicians were adequately interviewed; 25 had either personally observed severe shock or death or knew of such cases among colleagues in their home towns. For obvious reasons names and addresses were not asked, but as much information as could be was obtained from each informant.

TABLE LXIV.—METHOD OF ADMINISTRATION OF SUBSTANCES CAUSING SHOCK*

SUBSTANCE	NUMBER OF CASES	INTRAMUSCULAR	INTRAVENOUS	ORAL	INHALATION	ENDERMAL	SUBCUTANEOUS	SCRATCH	TRANSFUSION	UNKNOWN	OUTCOME		
											FATAL	RECOVERED	UNKNOWN
Serum	35	10	12			1	12			10	11	13	11
Morphine	1						1						1
Bee sting	4											4	
Milk	12	1		1							1	1	
Pollen (Bermuda grass)	1						1				1		
Glue	1					1					1		
Egg white	12					12					12		
Sodium iodide	1		1									1	
Bismuth tartrate	1		1								1		
Rabbit hair	1				1							1	
Green peas	1			1							1		
Quinidine hydrochloride	1		1									1	
Walnut	1							1				1	
Buckwheat	1					1							
Rye	1							1					
Feather extract	1		1									1	
Cold vaccine	1						1					1	
Wasp sting	12												12
Blood	12								12				
Ovomucoid	1					1					1		
Aspirin	3			3							3		
Hydatid cyst punctured	4												
Gum acacia	1		1									1	

*Cases gathered from the literature.

Systemic reaction vs. constitutional reaction.—Two types of cases were excluded: those that had been reported in the literature, and those of what we term "severe allergic reaction." A severe case of urticaria or even asthma following the administration of an overdose of pollen extract is a severe allergic reaction but is not shock. We feel that allergic shock is a much more explosive affair, developing with extreme rapidity, once it has started, and due in all probability to a quite generalized tissue edema, including interstitial edema of the lungs, and to almost universal increase in capillary permeability. The mechanism is probably quite similar to that responsible for urticaria and differs principally in its extremely widespread distribution. It should be borne in mind that the capillaries of the muscles alone in the aver-

age man have a total area of approximately 6,300 square meters, or more than 3,000 times the area of the entire body surface. It has been stated that in the absence of restraining forces, the entire plasma volume could pass from the capillaries into the body tissues within ten seconds.

TABLE LXV.—INSTANCES OF SHOCK IN SURVEY BY VAUGHAN AND PIPES

Cases of Severe Anaphylactic Shock or Death

SUBSTANCE CAUS- ING REACTION	MODE OF AD- MINISTRATION OR CONTACT	SHOCK	DEATH	SUBSTANCE CAUSING REACTION	MODE OF AD- MINISTRATION OR CONTACT	SHOCK	DEATH
	<i>Serums and Antitoxins</i>				<i>Foods by Mouth</i>		
Horse serum	Subcutaneous	3	1	Milk	Ingestion	2	
Horse serum	Not known		1	Eggs	Ingestion	2	
Tetanus antitoxin	Intramuscular	1		Beer	Ingestion	1	
Tetanus antitoxin	Not known	1		Wild honey	Ingestion	1	
Tetanus antitoxin	Not known		1	One cherry	Ingestion	1	
Diphtheria anti- toxin	Therapeutic	2		Blackberry pie	Ingestion	1	
Diphtheria anti- toxin	Therapeutic		2	Honey	Ingestion	1	
Diphtheria anti- toxin	Prophylactic		2	Soy bean	Ingestion	1	
Streptococcus anti- toxin	Intravenous	1			<i>Drugs</i>		
Scarlet fever anti- toxin	Not known	1		Quinine	Orally	1	
Antipneumococcus serum	Not known	1		Aspirin	Orally	3	
				Novocain	Intraurethral		1
				Iodized oil	Intraurethral	1	
				Calcium glu- conate	Intravenous	1	2
	<i>Pollen Extracts</i>			Neosarsphena- min	Intravenous	1	
Ragweed extract	Therapeutic	7			<i>Biologicals</i>		
Ragweed extract	Therapeutic		2				
Timothy extract	Therapeutic	2					
Rose pollen extract	Therapeutic	1		Antuitrin "S"	Subcutaneous	1	
	<i>Extracts for Allergic Testing</i>			Colon bacillus vaccine	10,000 dose, intravenous	1	
Ragweed	Scratch test	1		"Brooks hemo- protein"	Subcutaneous	1	
Wood smoke ex- tract	Scratch test	1		Liver extract	Intramuscu- lar	1	
Orris root	Scratch test	1		Pecan extract	Therapeutic	1	
Streptococcus vac- cine	Intracutaneous	1			<i>Insect Bites</i>		
Pure lactalbumin	Intracutaneous	1		Bee sting	Bite	4	2
House dust	Intracutaneous	1		Wasp sting	Bite		1
Horse serum (un- diluted)	Intracutaneous		1	Bedbug	Bite	1	
Annual sage pollen	Intracutaneous	1			<i>Transfusion</i>		
Mule dander	Intracutaneous	1					
Tetanus antitoxin	Intracutaneous	1		Egg in donor's diet	Intravenous	1	
				Milk in donor's diet	Intravenous	1	
					<i>Physical Allergy</i>		
				Sunlight	Prolonged ex- posure	1	

Blackshear who served in the British Army during the World War observed a surprisingly large number of sudden deaths after tetanus antitoxin injections. Each soldier who had been injured in the field received prophylactic tetanus antitoxin each time that he went into hospital. When transferred to successive hospitals, by the time they had reached base hospital, some had had

a number of injections at varying intervals. When death occurred on these later injections it was not with asthma but with generalized edema.*

With this in mind persons were asked particularly regarding the presence or absence of urticaria and asthma. While some of those interviewed were uncertain, the number who stated definitely that the symptoms were not inaugurated with urticaria or asthma was surprisingly large. This corresponds with Waldbott's conclusion that the local pulmonary reaction in shock is with pulmonary edema rather than asthma.

Some reactions, notably those to drugs, are probably not allergic but are included for general interest and because they were mentioned.

In an effort to provide some sort of a check on these random interrogations and to see whether sampling of a slightly different type of population would give materially different frequencies, the procedure was repeated at the meeting of The Medical Society of Virginia. Twenty-five physicians were interrogated, of whom 14 described cases of shock.

The information obtained is briefly summarized in Table LXV.

Some of the more interesting cases in this series have been described elsewhere in this volume. The reactions to serums and antitoxins, drugs, biologicals, insect bites and transfusions have been described under the proper sections. The following additional classifications are of interest:

Reactions to pollen extracts.—A physician had been treating himself with prophylactic ragweed extract. He was toward the end of the series. He had a typical shock type of reaction without urticaria, hay fever or asthma. This commenced within five minutes after the injection. The physician stated that if he had waited five minutes longer he could not have left his chair to get the adrenalin. Relief followed adrenalin injection in ten or fifteen minutes. He has not taken any treatment since. He had taken courses of treatment for the five previous years, but had never obtained extremely good results.

A traveling man had been in the habit of rushing into various doctors' offices, getting the doctor to give him an injection of pollen extract and then promptly rushing back to his car and driving on. One day he followed this customary procedure in a small West Virginia town. After he was back on the road he went into shock. He at last managed to get to a farm house from where a physician was called.

A patient received his fifth injection of ragweed extract. He promptly went into coma and respiration ceased. He was pulseless. He eventually recovered. The doctor felt confident that this was psychic.

A patient was being desensitized with ragweed extract. Injections were given every third day. Within one minute after the fourteenth treatment he collapsed, with loss of sphincter control and coma. During recovery he developed hives. During shock pulse and respiration were slow. Treatment was given with adrenalin, with recovery in 30 to 60 minutes. The next day he was entirely himself again.

A man had been receiving perennial ragweed treatment with two injections monthly. He missed one dose and at the end of thirty days came in for treatment. He was given the usual 0.1 cc. of 1:33 concentration. He walked to his office five minutes away, where he promptly went into coma. He took an ephedrine capsule before losing consciousness and his assistant applied a tourniquet. One hour later he was quite all right. No adrenalin was administered.

A patient had been receiving injections of ragweed oil for ragweed dermatitis. On one occasion he went into shock which was followed by severe abdominal pain and extreme headache whenever he would raise his head, all of which lasted about five hours. He did not lose consciousness. There was little urticaria and no asthma. Following this his ragweed dermatitis was entirely cured for several weeks. Embolism may have caused this reaction, in part at least.

*Blackshear, T. J., Wilson, N. C. Personal communication.

A man was being desensitized with timothy extract, had left the doctor's office and was working beneath his automobile. He had typical anaphylactic shock and had great difficulty in getting out from under the car to procure aid. This was an early small dose of timothy extract.

A woman, aged 60, had received preseasonal and coseasonal pollen treatment for six or seven years, without benefit. After an interval of several years without treatment she saw a new doctor who gave her preseasonal and coseasonal treatment with very satisfactory results. A year later, at the onset of symptoms, she received 0.1 cc. of 1:10,000 mixed ragweed. This was from the same bottle that had been used the previous year. Within thirty seconds she was comatose and in convulsions. The coma lasted about five minutes. This was followed by slight urticaria and pronounced asthma. She remained seriously ill for an hour and a half. Following this one episode she had no further treatment for the season and had no hay fever. One year later, during the season, she had 10 or 11 coseasonal injections with good results.

A case of anaphylactic shock occurred during desensitization therapy with extract of rose pollen. This was early in the treatment, the third injection.

Vander Veer, Cooke and Spain (1927) reported 96 constitutional reactions in 14,280 therapeutic pollen injections; Waldbott and Ascher (1936), 141 in 51,036 injections; and Furstenberg and Gay (1937), 75 in 29,547. Pollen extracts are more likely to cause reactions than other inhalant extracts, taken as a group. Thus Furstenberg and Gay observed only 2 constitutional reactions among 7,744 injections of the latter. None in any group was fatal.

Reactions to allergy test materials.—A negro orderly in a hospital who received a scratch test with 3 per cent ragweed extract collapsed and went into coma within three minutes. Blood pressure was 85. Pulse was rapid and thready. Respiration was normal. He remained unconscious for 30 to 45 minutes. He was treated with adrenalin. Late in the period of collapse, before complete recovery, he developed urticaria. There were no nasal or bronchial symptoms. During the preceding three years he had had coseasonal treatment with perfect results, receiving only three or four injections each season.

The wife of a farmer inhaled large quantities of smoke when the barn burned down. Thereafter she would have attacks of asthma when wood fires were lighted in the fireplace. She was tested with extract of wood smoke. Extract of wood smoke is prepared commercially for the curing of ham. Following the scratch test she promptly went into collapse but recovered.

In another case, scratch test with streptococcus vaccine had been negative. The same material was then tried intracutaneously. A systemic reaction followed within sixty seconds. This was accompanied by asthma and urticaria. It lasted for two hours and required a total of 3 cc. of adrenalin for relief.

An intracutaneous test with 0.05 cc. of concentrated horse serum, preliminary to the administration of antitoxin, resulted in death within five minutes. There had been no previous scratch test.

An intracutaneous test with 1:10,000 dilution of annual sage extract promptly resulted in a very strong intracutaneous reaction with generalized itching, generalized urticaria, brassy cough, asthma, blood in the sputum and vomiting. Adrenalin was given every 50 minutes throughout a period of 24 hours. The reaction was followed by anuria, after which so much albumin appeared in the urine as to produce a solid clot in the test tube. The patient received a total of 60 injections of adrenalin. The physician expressed it: "All of her mucous membranes were involved including the kidneys."

Deaths from endermal skin tests have been reported by Baagoe (egg white), Cooke (glue) and by Lamson (ovomucoid, buckwheat).

Reactions to foods. A doctor described two instances of collapse in infants when first given cow's milk. In each case the child vomited, became very pale and the family thought he was dead. One of these children had no hives, the other had hives during recovery only.

A case of anaphylactic shock was described following the eating of egg. This boy had been to a Thanksgiving dinner and ate mashed potatoes to which egg had been added. The child went into coma. Two or three doctors were called. Three hours elapsed before recovery.

A man allergic to ragweed went into shock without asthma or urticaria after eating wild honey. The physician is of the opinion that it was due to the ragweed pollen in the honey. It is well known that bees deposit quantities of pollen in honey.

After eating a single cherry a woman promptly experienced angioneurotic edema of the mouth and edema of the larynx. She had had a similar experience from a blackberry pie. Adrenalin gave relief on both occasions. This was early in the days of adrenalin therapy and the physician gave her 2 minims of 1:1000 intravenously. Thereupon he thought that she died. "She stiffened out, took a long breath, and was all right."

Shock due to physical allergy.—A woman extremely reactive to sunlight was preparing to take a bath. Unclothed, she answered the telephone in an upstairs sun room. She stood in the direct sunlight for some time and then went into collapse.

Discussion.—Some of the cases listed may not have been instances of allergic shock. Some may have been psychic, embolic, vasomotor, etc. It seems probable that a poll of physicians sufficiently large to possess statistical value would show a lower frequency, but the fact that 50 per cent of those interviewed had either seen or had first hand knowledge of severe reactions of this sort would indicate that they are much more frequent than the literature would lead us to believe. In any event, all physicians who have occasion to give percutaneous medication, especially of allergen material should realize that the possibility of shock reaction exists and should take all available precautions to prevent serious consequences.

Prevention

Appropriate steps for the prevention of constitutional reactions have been discussed under pollen therapy and serum disease. The first requisite is a realization that constitutional reactions may occur, more particularly in these two forms of allergy and in drug allergy; that reactions have been known to occur early in the course of hyposensitization even with a pollen extract dilution as high as 1:10,000. Fortunately such occurrences are rare but they justify the use of proper precautions from the very onset of treatment.

One should be conversant with the patient's allergic history, should know of any idiosyncrasy to foods, drugs or sera; of any allergic symptoms from exposure to horses or from any other cause; and even in the absence of this, should know of any family history of outspoken allergy. One should inquire concerning previous serum injections and their nature. Indeed any form of earlier percutaneous therapy should be discussed. Positive history does not preclude treatment but warrants caution.

Reactions have followed endermal testing and there have been at least two serious reactions from scratch testing. One should therefore use available safeguards in testing. With the exception of those allergens which have never been known to cause fatal reactions from skin tests, notably bacteria and fungi, the writer always performs scratch tests prior to endermal tests. It should be noted that a reaction to streptococcus vaccine was mentioned above. This program has the added advantage that in the absence of the positive scratch reaction, the strength of the endermal material may be increased, promoting more reliable tests.

The conjunctival test is also available and should be used, particularly in serum therapy.

The number of fatal accidents accompanying serum or other allergen therapy is probably far less than are deaths from anesthesia and elective surgery. However, an analysis of those deaths that have occurred has given

us the necessary knowledge with which to prevent repetition. Thus the program for serum desensitization is based on the allowance of a wide margin of safety beyond the circumstances attending published fatalities. These were: (1) death has followed the giving of one drop of undiluted serum intravenously; (2) it has followed endermal testing with 0.05 cc. undiluted; (3) it has occurred at the changeover from hypodermic to intravenous desensitization. The first 10 cc. is the critical quantity, beyond which one may proceed more rapidly. Future accidents should become increasingly infrequent, although the very rare case of extreme sensitization may continue to give trouble.

Systemic reactions (asthma, nasal response, urticaria, gastrointestinal symptoms) continue to appear unexpectedly during the course of desensitization even when all precautions are employed. True constitutional reactions (prompt shock with or without predominant localizing symptoms in these various systems) usually results from some error in procedure. The writer feels that there is need for a differentiation between these two types, both of which have as a rule been termed constitutional reactions. Failure to differentiate the two probably accounts in part for the wide variation in the incidence of constitutional reactions as recorded by Alexander from his interrogatory of practicing allergists. He received reports of anywhere from 1 per cent constitutional reactions in pollen therapy to over 11 per cent. One contributor described 68 per cent in his cases. Fifty-two allergists reported constitutional reactions in less than 1 per cent, while 35 reported them in from 1 to 10 per cent and 4 in over 11 per cent. Since they were all men of ability it seems probable that there was variation in the interpretation of the term. In any event the need for constant watchfulness is obvious.

Causes of Shock and Their Avoidance

The chief causes of trouble are as follows:

1. Failure to anticipate potential trouble.
2. Too rapid desensitization, either with injections given too frequently or the size of the dose increased too rapidly.
3. The "chancing" of short cuts usually due to unnecessary haste.
4. Administering the wrong concentration through error.

Inasmuch as these factors have been discussed in detail under serum therapy the following discussion will apply particularly to pollen therapy, the other chief source of systemic and constitutional reactions.

Too high an initial dose.—Occasionally constitutional reaction occurs at the first dose. Ninety-five to 98 per cent of pollen allergies will tolerate an initial dose of 0.1 cc. of 1:5,000 (20 Noon units). Clowes (1913) reported the first constitutional pollen reaction occurring in America, hay fever, vertigo, and generalized discomfort following injection of 1 cc. of 1:50,000 ragweed extract (20 units).

As a rule, but with exceptions, such extreme reactors respond to skin testing with very strong reactions. In the presence of unusually intense test reactions the initial dose should be reduced to 1 or 2 units or even less.

Too rapid treatment.—Cohen and Rudolph have shown that pollen allergen continues to be present as such in the blood for at least 48 hours. Preseasonal therapy with increasing doses given oftener than every third day may therefore conceivably result in cumulative action. The only way to be certain that

this does not occur is to give injections not oftener than every third day, even though the short time available before the onset of the season supplies the urge to more rapid desensitization. This does not necessarily mean that injections cannot be given more frequently, but when they are, vigilance should be increased.

Too rapid increase in dose.—The factors considered in the preceding paragraph apply equally here. Often it is possible to increase the early smaller doses more rapidly, slowing up as one approaches the high concentrations. However, it should be borne in mind that reactions may occur with any of the concentrations, with practically any of the dosages customarily used. Patients who with treatment in previous seasons have had no systemic or constitutional reactions will probably tolerate rapid increase better than those who have shown a reactive tendency.

Deterioration of extract.—This occurs especially in perennial therapy, when one is using an extract which allows rapid deterioration. Most extracts which do not contain glycerin lose considerable potency within a three month period. When one uses up a bottle of a certain original strength and changes to a freshly made extract, of the same original strength, one may be actually changing to a much stronger extract. Methods of avoiding this difficulty have been discussed under Perennial Pollen Therapy.

Change of concentration of extract.—Furstenberg and Gay found that reactions are more likely to occur at the change from a large volume of a weaker extract to a small volume of a stronger extract, in spite of careful standardization of the extracts. A safe precaution when changing to a higher concentration is to repeat the last preceding dose (in terms of units). Thus, if the next concentration is 10 times as strong, the first dose should be one-tenth (by volume) of the previous more dilute one.

Use of the wrong antigen.—When one is treating a number of persons with different sensitizations and the bottles of extract are all kept together, one might through error pick up the wrong bottle. The writer had such an experience. A patient was strongly allergic by skin test to English plantain and ragweed. Symptoms were attributed to English plantain, since they began before the onset of the ragweed season and terminated before its end. This patient had been given two years of perennial English plantain treatment with excellent results. Coming in for her regular maintenance injection of 0.2 cc., she was tested again with both plantain and ragweed, for the purpose of determining whether plantain desensitization would tend to make a positive ragweed reaction disappear. She was still strongly positive to both. With ragweed evidently uppermost in my mind, I then proceeded to give her a maintenance dose, but from subsequent events it seems probable that instead of plantain, she received 0.2 cc. of 1:50 ragweed extract. Two hours later the arm commenced to swell, becoming about twice normal size. There was local urticaria. The probable error was then realized and treatment was given with adrenalin and cold applications. Fortunately no other symptoms developed. The swelling subsided after about 48 hours.

It seems probable that others have had similar experiences, for Aaron Brown has devised a procedure designed to aid in preventing such accidents. This consists in the use of rubber caps of various colors on the bottles of allergens. Red caps are used for weeds, green caps for grass pollen, blue caps

for tree pollens, and yellow for food extracts. He states, "since this introduction, error in picking up a timothy extract bottle, for example, instead of one of ragweed, has been eliminated."*

The customary procedure in ragweed hyposensitization is to use a mixture of giant and short ragweed, usually in equal parts, irrespective of the relative prevalence of the two weeds in the vicinity. This is justified by the fact that the antigens appear to be identical or nearly so.

However, the observations of Hebard and Barnard suggest a good reason for using short ragweed rather than giant. They observed that patients who had been receiving giant ragweed, when given the same dose of short ragweed extract, often experienced constitutional reactions. The reverse was not true. This increased capacity to produce constitutional reactions was not reflected in the skin tests. Both produced equally strong cutireactions. They found the neutralizing capacity of short ragweed much greater than that of giant ragweed. The difference appeared to be quantitative rather than qualitative. They believe that either extract will protect patients having ragweed hay fever but that with short ragweed extract, maximum tolerance will be reached with a much smaller dose. We should state, however, that as yet it has not been determined that this is necessarily a desirable accomplishment.

Several years ago Aaron Brown reached different conclusions, that the two pollens were identical and interchangeable. However, Brown's top dose was much lower than that used by Hebard and Barnard. The latter observed the constitutional reactions with higher doses.

For the present it seems logical to continue with the use of equal parts of both allergens.

Use of the wrong concentration.—I have heard of fatal reactions following the giving of concentrated extract, through error, at the beginning. Such an error occurred once in my own clinic; however it was fortunately not fatal. A patient with ragweed hay fever came in for her first treatment just as I was leaving in response to an urgent summons. I directed a technician who had not previously seen this patient to give her 0.05 cc. of 1:5,000 ragweed extract. The patient received her treatment and departed. After she had gone three or four blocks she broke out with universal hives and experienced a tremendous pounding, throbbing in her ears. She returned to the office as quickly as she could where she was given adrenalin, a tourniquet was applied, and she was given ice rubs. She recovered completely in the course of about two hours. Upon my return I discovered that she had been given 0.05 cc. of 1:50 ragweed extract. I was confident that I had said 1:5,000 and the technician was equally so that I had said 1:50. Probably she was right. Since then it has been an unvarying rule in our clinic that the physician himself gives pollen and similar extracts. In this way the possibility of confusing an order is eliminated.

Furstenberg and Gay observed 9 outright mistakes over a 6 year period, with about 30,000 injections, in a busy clinic. Only 5 of the 9 overdoses resulted in constitutional reactions. Erroneous overdosage probably accounts for but a minority of constitutional reactions.

Rice describes an experience in which the increase in dose was tremendous. The patient was receiving coseasonal treatment with 0.02 cc. of 1:10,000 ex-

*Available through the National Surgical Supply Company, 458 Broadway, New York N. Y.

tract of acnida, pigweed, short and giant ragweed. Through error the dose was suddenly increased to 0.04 cc. of 1:10 concentration. The patient immediately complained of intense burning at the site of injection. The tourniquet was already in place on the arm and a blood pressure cuff was substituted therefor. Epinephrine was injected surrounding the site of the administration of the extract and for the next hour pressure on the cuff was relieved for only a few seconds at a time. Epinephrine was administered in the other arm and a tourniquet was placed above it to control symptoms of adrenalin overdosage. After some time the cuff on the treated arm was released for forty seconds with resulting immediate violent hay fever with complete closure of the nose and injection of the conjunctivae.

The cuff was kept in place for four hours. During this time it was released from time to time for intervals of from 30 to 90 seconds. Following each release of antigen there was a release of epinephrine into the general circulation from the opposite arm. The patient experienced no asthma at any time, his outstanding symptoms being nasal stoppage and mild urticaria. Half an hour after the cuff was removed (at the end of 4 hours) the patient went home. He felt perfectly well, nose and eyes were symptom free, and only a few wheals remained. That evening he had a mild attack of urticaria which required no treatment. His arm was very sore for two days but there was no further general reaction.

Piness has devised a system which would tend to minimize errors in selecting concentrations. He uses different colored labels for the various concentrations, the highest being red.

Unnecessary activity by the patient after treatment.—Clinical experience indicates that strenuous physical exertion after an injection will increase any tendency toward systemic reaction. Systemic reactions are also likely to occur on very hot days. The patient is therefore well cautioned, to avoid unusual exertion and overheating for the first two hours following injections.

Accidental penetration of a venule.—There is the possibility of a subcutaneous injection entering a venule and becoming thereby an intravenous injection. Waldbott suggests the term *back-seepage reaction* as indicating trauma to a vein with consequent back-seepage into the blood stream. A slight tug on the plunger of the syringe after the needle has pierced the skin as recommended by Bernton will show whether the point is at a location where blood may be drawn. If so, the needle should be withdrawn and inserted elsewhere.

Exceeding of patient's individual tolerance.—Some persons are more prone than others to react with systemic or constitutional symptoms. Fourteen of 21 patients with constitutional reactions studied by Furstenberg and Gay had more than one constitutional reaction. Six had four reactions each and 3 had even five.

A small proportion of pollinosis cases will not tolerate the high doses that are customarily given just prior to the season. When reactions occur one may drop back slightly and again attempt to increase the dose, but some will continue to react, thus indicating that their tolerance has been exceeded. In such an event it is better to be content with whatever protection has been achieved, rather than to force higher dosage. If relief is not adequate, coseasonal treatment may be used also.

Cause unknown.—Furstenberg and Gay were unable to discover any cause for the constitutional reactions in one-half of the “clinic group” of 50 patients or in two-thirds of their 25 private patients.

Failure to use available safeguards.—If injections are given into an extremity a tourniquet may be applied in the event of reaction, above the site of inoculation. Injections elsewhere automatically dispense with this possible safeguard.

Adrenalin should always be immediately available.

It has been our custom when sending pollen extract to the attending physician, to enclose the following series of instructions for allergen administration:

Directions for the Avoidance and Control of Reactions

As a rule there is no reaction associated with the administration of allergen extract. When done incorrectly, reactions sometimes occur, and they may be severe. A reaction may occur any time up to two hours or longer after an injection but the severe reactions usually take place within the first twenty or thirty minutes. The symptoms start as urticaria (hives), violent sneezing or asthma. Occasionally the first symptom may be syncope. A reaction means that too large a concentration of the allergen has reached the blood in too short a time. It may be due to the use of too large a dose or to the hypodermic needle entering a minute blood vessel. The following technic will control reactions that occur in the proper administration of allergen extract.

1. Make certain that the bottle of extract which you have picked up is the proper concentration.

2. Withdraw into the syringe the correct amount of extract.

3. Introduce the needle, running it under the skin, at an angle, for a distance of about one-half inch.

4. Tug on the plunger before injection. If blood appears, withdraw the needle and try elsewhere on the arm. If no blood appears, give the injection.

5. Have the patient wait at least thirty minutes in the office after each treatment. Bear in mind that the symptoms of reaction are itching of the skin with urticaria, violent sneezing or asthma.

6. Before the patient is allowed to go be sure that he has with him some tablets containing propadrin, one-half grain with theophylline, four grains which he can take in the event of appearance of symptoms after leaving office. Tell him, in this event, to take a tablet and then get in touch with you immediately. Ephedrine capsules may be used but act more slowly.

7. Direct the patient to avoid strenuous exercise or becoming overheated for at least two hours after an injection.

8. Allergen extracts are best given in varying locations. Some allergists just alternate the arm while others use three different sites on each arm before returning to the first site. If this is done care should be taken not to get the highest of the three sites so high on the arm that a tourniquet cannot be applied above.

9. Reactions are most likely to occur when injections are given frequently. It has been shown that allergen continues to circulate in the blood for more than twenty-four hours but less than forty-eight hours. Thus with the rapid method of administration (daily or twice daily as is sometimes necessary in coseasonal treatment) there is a greater tendency to reaction and this must be more carefully guarded against.

The subcutaneous reaction which is not infrequently observed on the day following an injection is of no significance. It consists of a red, swollen, hot, tender area around the site of inoculation which may occasionally extend over an area the size of the palm of the hand or larger. It looks like an infection but is not and will subside in twenty-four or forty-eight hours. If very uncomfortable an ice cap may be applied. Most patients do not have any great degree of subcutaneous reaction.

Treatment of Reaction

In the event of an anaphylactic reaction through failure to carry out carefully the above program or for any other reason, the following measures are applied.

1. Let the patient lie down and immediately apply a tourniquet above the site of the inoculation. Inject one half cc. of 1:1000 adrenalin into the other (unused) arm and then

one-third cc. into the site of inoculation. Usually the patient will begin to improve within sixty seconds and will soon become comfortable. He will then develop adrenalin symptoms (palpitation, possibly headache, nervousness, tremor). When he does this let up on the tourniquet so as to let a little more of the allergen into the circulation to combat the adrenalin effect. Replace the tourniquet with a sphygmomanometer if available. Otherwise continue to use the tourniquet.

2. If anaphylactic symptoms begin to return, blow the sphygmomanometer up to about 100 millimeters and keep it there until the anaphylactic symptoms are again relieved and adrenalin symptoms have reappeared. Then let the air out of the sphygmomanometer but leave it in place to be blown up again shortly. Be sure that the entire cuff is above the site of inoculation.

3. Repeat this process of alternation between adrenalin effect and anaphylactic effect until the pressure can be let off the cuff permanently without return of asthma, hives or sneezing. The cuff may also be loosened for a short time if the fingers go to sleep. The advantage of the sphygmomanometer is that the pressure can be controlled so as to shut off venous return without completely shutting off arterial supply. In this way the hand will not "go to sleep" as quickly.

4. It is well to take the blood pressure from time to time. If it is elevated the patient is under adrenalin effect, and if it is subnormal he probably has some anaphylactic shock. This might indicate the need for another dose of adrenalin in the unused arm. Also adrenalin may be repeated in the untreated arm (the arm without tourniquet), if symptoms have not been promptly relieved.

5. It is well to take the temperature and if, as rarely happens, it is elevated an ice wash of the entire body will help. Ice cold compresses on the spots of urticaria help.

6. Sometimes as long as one or two or even three hours may be required before the tourniquet or sphygmomanometer may be permanently removed.

7. In the event of a reaction following an injection even though mild the next injection should not be increased but should be made smaller and the patient should be kept in the office a little longer.

Occasionally a patient will be found who will for some reason tend to react, usually mildly, to every injection. When this occurs it is well to give 0.1 cc. of adrenalin, 1:1000, and 0.1 cc. of 3 per cent ephedrin, with each injection of allergen. The adrenalin and ephedrin may be kept mixed for this purpose, but should not be mixed with the allergen until just prior to use. In this case add 0.2 cc. of a mixture of equal parts of the ephedrin and adrenalin solutions. Suck the adrenalin and ephedrin into the syringe *first*, followed by the allergen, in the same syringe.

Effect of Constitutional Reaction on Results of Treatment

By analogy to the experimental state known as antianaphylaxis, a person who has experienced a systemic or constitutional reaction and recovered should theoretically have become more nearly desensitized than others under treatment and more likely to be relieved of symptoms during the ensuing days or weeks. Actually, we observe not infrequently that such a person does surprisingly well during a pollen season, if systemic reaction occurred but a short time before the onset of the season or during the season. In such cases one might reason that the anaphylactic reaction has stimulated the protective reactive mechanism of the body to at least temporarily greater effectiveness in its adjustment to a deleterious environmental factor, the pollen. The process may be similar to that occasionally responsible for improvement for a period after an acute infection or surgical operation. Or one may explain it chemically in terms of saturation of antibodies.

Therapeutic improvement of this sort does not always follow systemic or constitutional reaction. Often one's pollinosis continues unaffected except as by subsequent therapy. I do not recall having observed subsequent exaggeration of symptoms that could be attributed to the reaction.

Allergists have speculated on the therapeutic possibilities of a single top dose, if the highest dose could be given first. Experience has shown that this

is impossible, but it is interesting to wonder whether, if one could give a maximum therapeutic dose at the beginning of treatment, any other treatment would be necessary at all. Rice's case described above is one in which this was almost accomplished. Three days after this large dose the patient's hay fever returned. Treatment was recommenced with the 1:10,000 concentration. This was given through the remainder of the season with satisfactory relief.

It would appear from the evidence that a single top dose would not protect for any great period. One might argue that this patient was protected against having a constitutional reaction by the emergency treatment, but the fact remains that he did receive a very large dose and did have some constitutional symptoms. One might argue that the adrenalin obscured the issue, but to this we can answer that Duke recommends the administration of adrenalin or ephedrin or both with every preseasonal injection as the dose is being gradually increased, and that his results are presumably as good as those he had previously obtained with antigen alone.

In preseasonal treatment one must reach an adequate top dose prior to the onset of the season, for best results. This dose ranges from 0.5 cc. to 1 cc. of a 2 per cent solution, more usually the latter.

The 0.05 cc. of 1:10 concentration administered by Rice should correspond to the writer's customary top dose of 1 cc. of 1:50, and yet this relieved his patient for no longer than the previous 0.02 cc. of 1:10,000. A single top dose, apparently, will not work satisfactorily. Furthermore there would be no superiority in giving a single top dose at the onset of the season when a perfectly safe coseasonal dose does just as well.

Clark and Leopold have analyzed a series of 612 persons receiving prophylactic ragweed treatment during the period 1921 to 1936. Only 3 per cent of those completely relieved experienced constitutional (systemic and constitutional) reactions during the course of treatment; 7.7 per cent of those greatly relieved and 11 per cent of those moderately relieved experienced similar reactions. This would suggest that the fewer the reactions the more likelihood of better results. Unfortunately this suggested sequence failed in the final group, those experiencing little or no relief, among whom only 4.5 per cent had reactions. This series would indicate that the occurrence or nonoccurrence of systemic reaction is of little importance as regards ultimate benefit. The analysis does not indicate the stage of treatment at which the reactions occurred.

Status Thymicolymphaticus

Waldbott has repeatedly suggested that the condition known as status thymicolymphaticus may be associated with allergy. Although this suggestion has been by no means generally accepted, his observations are sufficiently suggestive to warrant further study. The difficulties inherent are obvious. As he states, the diagnosis of status lymphaticus usually cannot be definitely established before death, and after death clinical and immunologic investigation is impossible. He marshals the indirect evidence suggesting a possible association between allergy and status lymphaticus as follows:

Among 15 cases with anaphylactic shock following serum injections 8 were reported to have had enlargement of lymphoid structures. In 8 asthmatic deaths reported by MacDonald enlargement of the thymus and lymphoid structures was recorded in all. Huber and Kessler have also noticed such changes. In 20 cases of sudden death after local

anesthesia, thymic hyperplasia was present in 11. In 26 cases of sudden death during general anesthesia 10 had thymic and lymphoid hyperplasia. Waldbott evidently assumes that these deaths are allergic. He reports x-ray evidence of enlarged thymus in a number of allergic children whose asthma began immediately after birth. He reports cases of sudden death in children of allergic families, particularly asthmatic families. He calls attention to the parallelism in the old description of status lymphaticus and the present-day description of the allergic constitution. Symptoms common to both are chronic upper respiratory catarrh, gastrointestinal upsets, eczema, eosinophilia.

He states, "While none of these facts are in any way conclusive, they are nevertheless sufficient to stimulate investigation into the possible association of status thymico-lymphaticus with status asthmaticus and the relationship of thymic death to anaphylactic shock."

Graham and I have observed a high incidence of palpable superficial lymph nodes in allergies, both adults and children.

PART XII

DRUGS

*An open foe may prove a curse,
But a pretended friend is worse.*

—GAY

CHAPTER LXV

DRUG ALLERGY

“The separation of the drug allergies from those due to agents not used in medicine has no reason based on any special constitutive nature of the substances classed as drugs, and we shall see that there are no peculiarities in the clinical manifestations of the drug idiosyncrasies sufficient to stamp these as essentially different, in their underlying mechanism, from the idiosyncrasies to the non-medical substances—food or other. The separation is, in fact, upheld chiefly by custom and also by a certain convenience to the student of the general subject of idiosyncrasy.”

As stated above by Coca, there is probably no basic difference between drug allergy and the other forms of idiosyncrasy. The basic processes are probably similar or identical. The separate classification is justified because (1) it represents a different type of excitant, nonprotein; (2) it is the first in which the possibility of hapten activity was studied; and (3) it represents a phase of allergy in which the physician must at times assume great responsibility in his efforts to ameliorate rather than exaggerate the patient's illness.

We have seen that each new group of possible allergic excitants after that first recognized (protein) has caused considerable debate before acceptance within the classification. Drugs in which protein played no apparent part were the first. They caused symptoms which in general resembled those of allergy and which were very much the same, no matter what drug was responsible.

Pharmacologic studies have established definite normal actions for different drugs. While morphine diminishes pain perception, contracts the pupils, slows respiration, and increases muscle tone in the intestinal tract, atropine dilates the pupils, stimulates the central nervous system and causes smooth muscle relaxation in the intestinal tract. The pharmacologic activities of these two drugs are altogether different. But one who is allergic to them may react to either with the same symptoms. These are the symptoms commonly observed in allergy.

Allergy vs. hyperergy.—This altered response to a drug is to be distinguished from an exaggerated normal response such as is observed in drug intolerance or hyperergy. Such a person reacts in a normal manner but to a

much smaller dose than normal. In the writer's experience it is not unusual to observe drug intolerance in otherwise allergic persons sensitized to foods, inhalants, etc. I have made no study to determine whether hyperergy is more frequent in allergies than in nonallergies although I have rather suspected that it may be. Not infrequently an allergic with drug intolerance will have found from experience that a number of drugs produce toxic symptoms. This is the type of patient who will announce that nearly everything the doctors do for him seems to make him worse. An extreme example is the following. A young married woman with allergic migraine, urticaria and colitis was intolerant of nitrates, nitroglycerin, belladonna, hyoscyamus, ephedrin, cod-liver oil, viosterol, and ergotamine tartrate. Only belladonna, ephedrin, cod-liver oil and viosterol caused allergic responses. The reactions to the remainder were of the hyperergic type.

Acquisition of sensitization.—In drug idiosyncrasy as in serum disease the question arose as to whether we are dealing with a condition which is basically different from that of experimental anaphylaxis. In many cases careful investigation of the history suggested that allergic symptoms appeared following first contact with the drug, without a preliminary or sensitizing contact. This raised the question of an inheritance of the idiosyncrasy. However, the possibility of hematogenous intrauterine exposure or exposure through breast milk, combined with the fact that an antecedent exposure in the normal way is often hard to trace or recall, make the question of heredity appear less important than it did at one time. The statement by Walzer that drug and chemical hypersensitiveness is an uncommon manifestation in babies and young children and that adults are those most frequently affected, suggests, very indirectly to be sure, the probability of a previous sensitizing exposure in most cases.

The conception of hapten combination of the drug with human protein following absorption to form a new allergen specific for itself and not for the proteins of the host, provided a rational explanation for the mechanism. The observation that once a person or animal is sensitized to the hapten-protein combination, the hapten alone may cause allergic reaction explains the rapidity with which symptoms may occur. Zinsser speaks of the hapten theory of drug allergy as "the only reasonable hypothesis that has been advanced to explain drug idiosyncrasies."

Classification.—Drugs may cause allergic reactions following absorption or through direct contact with the skin. It has been customary to discuss allergic skin reactions at the point of contact under "contact allergy." Although drugs may be responsible for contact allergy, we will here discuss only allergy to drugs which exert their action after penetration of the tissues. This may occur through the intestinal tract, respiratory tract, the urogenital system or following precutaneous administration, hypodermically, intramuscularly or intravenously. Absorption may even occur following topical application to the skin. Thus, systemic allergic reactions to belladonna have been described following the application of an ointment containing belladonna. This obviously should be classed as drug rather than contact allergy.

Symptoms.—Symptoms may follow the first recognized or traceable contact with the drug. Usually there is history of previous administration of

longer or shorter duration, often with an intervening period without the drug. At times symptoms which have been interpreted as allergic have supervened during a long course of drug administration, either daily or at frequent intervals, and without an intervening period of freedom from contact. In this case the allergic symptoms usually develop slowly, becoming more pronounced with continued contact. This is illustrated in allergy to neoarsphenamine, cinchophen and possibly also iodides and bromides. The evolution of such sensitization might be compared to the situation with daily ingestants such as wheat, egg and milk. The incubation period prior to the development of sensitization is very much the same as that in serum disease, having been recorded as varying from five to twenty days. Symptoms are generally those of the commoner allergies, including urticaria and the more chronic dermatoses, asthma, allergic coryza, migraine, gastrointestinal symptoms and, occasionally, shock. However, certain symptoms are especially frequent in drug allergy. These are fever, skin eruption and edema of the angioneurotic type. Furthermore, certain groups of drugs tend to cause reactions which are characteristic for themselves, and may be of diagnostic significance. The nature of symptoms depends upon the route of contact, the nature of the allergen and possibly also upon obscure factors in the patient's constitution. Thus, the arsenicals have an especial tendency to produce dermatitis which appears to be allergic and in certain individuals the reaction may also occur in the liver, with consequent hepatitis. These reactions may follow intravenous or intramuscular (sulfarsphenamine) introduction. The writer has seen two physicians who experienced asthma following the inhalation of minute amounts of the powder during the process of preparing solutions.

Joseph L. Miller has reported a similar case in a nurse following one month of exposure in her work, in whom a strongly positive skin reaction was observed. Symptoms were nausea, vomiting and asthma. Klauder has seen a case in a physician with asthma and eczemoid dermatitis from contact and inhalation. Similar attacks have been described by Vuletic and by Szarvas.

Symptoms Characteristic of Drug Allergy in General

Fever.—This is probably the most frequent symptom. Certainly it is the most characteristic, since with the exception of serum sickness it occurs with much less frequency in the other forms of allergy. Antipyretics, customarily given to lower temperature, usually produce an increased temperature in those who are allergic to them. It may occur with or without eruption in quinine, iodine and mercury allergy. The temperature may be as high as 104 to 106°. Coca mentions a person with quinine allergy in whom the temperature reached 108 degrees.

The need for recognizing drug allergy as a cause for fever during the treatment of a disease which is in itself accompanied by fever is obvious.

Eruption. The eruption may take on numerous forms. It may vary at different times in a single individual reacting to a given drug. Urticaria is frequent, especially after aspirin. Erythema may be scarlatiniform. A morbilliform eruption or erythema multiforme may occur. Desquamation is occasionally a prominent symptom and it seems probable that some cases of exfoliative dermatitis have an allergic basis. This is true especially of the

arsenicals and has been described following intravenous sulfur medication. Herpetic lesions are especially frequent with arsenic compounds. Papular, pustular, nodular, vesicular and hemorrhagic skin lesions may occur. Skin pigmentation has been observed, particularly in the fixed type drug eruptions. It seems reasonable to assume that as more is learned of drug allergy, more of those dermatoses which today are readily diagnosed by virtue of their characteristic clinical pictures, but whose cause remains unknown, may be found associated with drug or some other form of allergy.

The dermatosis is usually pruritic. Occasionally pruritus is the only skin symptom. Fever may or may not accompany the dermatosis. Mucous membranes are rarely involved.

Other symptoms.—Other symptoms, as in serum sickness, include edema, especially of the face; swelling of the lymph nodes and swelling of the joints. Coca mentions local edema or sterile abscess or gangrene occurring at the site of injection. Such reactions in serum sickness have been described in the preceding chapter under Arthus phenomenon.

Leukopenia.—Heran and Saint Girons have reported hypotension and leukopenia following the administration of quinine to a quinine allergic. Robinson has found leukopenia characteristic of arspenamine allergy.

Granulopenia.—In 1922 Werner Schultz described five cases of a previously unidentified disease, accompanied by leukopenia in which the leukocytes fell to 1,000 or less, the decrease being due to disappearance of the granulocytic cells. By 1929, 152 cases of agranulocytic angina, also termed granulopenia, malignant neutropenia and agranulocytosis, had been reported. In 1933 Kracke noted that granulopenia first made its appearance not long after the use of synthetic hypnotics and aminopyrine became widespread. Aminopyrine was much better known by physicians and nurses than by the laity who were more in the habit of taking aspirin as an analgesic. Kracke called attention to the high proportion of cases of granulopenia occurring in doctors, doctors' families, nurses and druggists. Madison and Squier (1934) demonstrated allergy to aminopyrine as the etiologic agent. There have been a number of confirmatory reports although granulopenia has occurred when no aminopyrine or related drug was used. The hypnotics so far have been exonerated but we may say that although aminopyrine is the chief cause, other drugs may be responsible for some cases.

One such drug was soon found to be dinitrophenol. Cutting and Tainter (1933) had observed during the World War that employes in the munition factories exposed to quantities of dinitrophenol (a picric acid derivative) lost weight rapidly, often with accompanying fever. After careful study they reported upon its use in the treatment of obesity, its action appearing to depend upon greatly accelerated metabolism sometimes with associated pyrexia. Almost from the beginning toxic effects were observed, some of which were allergic in nature. Between six and seven per cent developed urticaria during the treatment which cleared up promptly after discontinuance. The drug came into rather wide use for a short period during which time deleterious side effects were observed, including granulopenia which was at times fatal.

Robinson performed leukopenic index studies on 25 persons allergic to arspenamine and on 25 controls. All of the controls showed negative in-

dices, except one, who after his second dose of arsphenamine showed a leukopenic drop of 1,500 and 2,000 on two different readings. However, two or three treatments after this, the patient developed allergy to arsphenamine with nausea, vomiting and dermatitis. All of the 25 known arsphenamine allergies gave positive results. One patient experienced a drop of 4,000. Control tests with physiologic sodium chloride gave a rise of a few hundred cells, in the counts.

Symptoms More or Less Characteristic of Certain Drugs

Arsenic and antipyrine are especially likely to cause herpes.

Digitalis, opium, chloral, antipyrine, salvarsan often produce swelling of the face.

Aminopyrine, dinitrophenol, occasionally the arsphenamines may produce granulopenia. Luminal often causes a morbilliform eruption.



Fig. 263.—Fatal dermatitis with associated stomatitis due to luminal. (Courtesy of Dr. Udo J. Wile.)

The antipyretics tend to produce fever.

Belladonna produces an urticarial or scarlatinal rash.

Arsenicals are especially prone to produce a scaly eruption and exfoliative dermatitis.

Phenolphthalein, the arsphenamines, antipyrine, phenacetin, salipyrine and the barbiturates are often responsible for "fixed drug eruptions."

The acneiform and nodular lesions associated with bromide and iodide medication are characteristic. Some writers consider these allergic, but clinically the picture is not clear cut, since dosage and duration of therapy appear often to play a part and, following re-exhibition, symptoms do not necessarily recur until after the drugs have been given over a rather considerable period. It may be that this rash should be considered more in the picture of hyperergy than allergy.

Cipollaro has listed the types of dermatologic reactions to a number of drugs as shown in Table LXVI.

TABLE LXVI.—TYPES OF CUTANEOUS RESPONSE IN DRUG ALLERGY

DRUG	TYPE OF CUTANEOUS REACTION
Acetanilide	Erythematous. Cyanosis of lip in cardiacs.
Antipyrine	Morbilliform, scarlatiniform, urticarial, or bullous. Maculo-pigmented, like phenolphthalein.
Arsenic (including the arsphenamines)	Herpetic, pustular, urticarial, keratotic, pigmentary, ulcerative. Death may result from exfoliative dermatitis or edema of the glottis.
Atabrine	Alopecia, eczema, exfoliative dermatitis, fixed eruptions, lichen planus- type eruption, lupus erythematous-like eruption, poikiloderma, and ungual changes and dystrophies.
Barbiturates	Urticaria, blood dyscrasias, purpura, fixed eruption, bullous lesions of skin and mucosa, morbilliform and scarlatiniform eruption.
Bismuth	Pigmentation of gums, stomatitis, erythroderma, scarlatinoid erythema, urticaria and pruritus.
Bromides	Acneform, furuncular, bullous erythematous, pustular and pustulo- squamous. May be local or generalized. Nodose and tuberos lesions.
Chloral hydrate	Papular, lichenoid, urticarial, purpuric, scarlatiniform and erythematous. Cyanosis of extremities and bullous (rarely).
Chloroform	Erythematous, purpuric.
Cinchophen	Angioneurotic edema, erysipelatous swelling of face, scarlatiniform, urticarial and eczematous, jaundice.
Copaiba	Scarlatiniform, followed by desquamation; papular and urticarial.
Digitalis	Scarlatiniform, erythematous and papular.
Ephedrine	Scarlatiniform, erythematous, eczematous, purpuric.
Insulin	Urticaria. Subcutaneous tumefaction at site of injection (lipodys- trophy).
Iodides	Acneform, pustular, carbuncular, vegetating, bullous, nodular, purpuric, papular, urticarial, and erythematous. May terminate fatally.
Mercury	Discoloration of gums, stomatitis, folliculitis, scarlatiniform, eczematoid and dermatitis exfoliativa.
Morphine	Erythematous, maculopapular and urticarial, pruritus.
Penicillin	Eczema (contact type), exanthems with symptoms of serum sickness, morbilliform, urticaria.
Phenolphthalein	Erythematous, urticarial, bullous, and erythema multiforme-like erup- tion, fixed, circumscribed and polychromatic pigmented lesions.
Procaine	Papulovesicular; verrucous condition of ends of fingers occurring in dentists.
Quinine	Erythematous, scarlatiniform, purpuric, urticarial, vesicular, bullous and ulcerative.
Salicylates	Erythematous, scarlatiniform, desquamative.
Sulfonamides	Angioneurotic edema, eczema (contact type), erythema multiforme-like eruption, exfoliative dermatitis, fixed eruption, purpura, scarlatini- form and morbilliform eruption, urticaria.

Fixed Drug Eruptions

These were recognized not long after antipyrine came into use (1885) as one of the cutaneous manifestations of idiosyncrasy to the drug. They were first clearly described and given the present name by Brocq (1894). Although a fixed drug eruption is often persistent, especially when contact with the offending drug is maintained, or frequently repeated, it is not in this sense that it is "fixed." It is the location on the body that is "fixed," or persistent.

The typical lesion appears as a rounded or oval edematous plaque with rather sharply demarcated margins, varying in size from a small coin to the palm of the hand, reddish in color, later becoming pigmented from the deposition of melanin. Bullae may form at the surface followed by desquamation or crusting. When fixed eruptions occur on mucous membranes, as in the mouth, on the genitalia and in the perianal region, they may appear as edematous or erythematous patches but more often are vesicular or pemphigoid, later breaking down, leaving superficial erosions.

While the circular pigmented area is most characteristic, a fixed eruption may take the form of simple localized urticaria always recurring in the same area, may be morbilliform, scarlatiniform or may appear as a recurrent localized erythema multiforme. In the latter case if it persists, pigment deposition follows. New areas may become involved. Occasionally a fixed drug eruption may be eczematous (erythematous, follicular, papular, vesicular, herpetic).

Unusual forms are: a recurrent conjunctivitis involving especially the lower outer quadrant of one eye; peripheral nerve involvement, usually in the form of recurrent localized neuritis; and a simple localized pruritus recurring in situ without eruption.

Abramowitz and Noun who have made an exhaustive review of the literature find that the following medicinal preparations have been reported as causing various types of fixed drug eruption.



Fig. 264.—Fixed drug dermatitis resembling Arthus' phenomenon, involving the right buttock with necrosis. Due to Midol taken for dysmenorrhea.

Acetphenetidine (phenacetin).

Acriflavine hydrochloride (trypaflavine).

Antipyrine, aminopyrine and its compounds.

Antimony and potassium tartrate.

Arsenicals: acetylarsan, arsphenamines, mapharsen, tryparsamide.

Barbiturates.

Bismuth salts.

Cinchophen (atophan).

Iodides.

Ipecac (emetine).

Ipomoea (scammony).

Isacen (diacetyldioxyphenylisatin).

Mercury.

Phenolphthalein.

Quinine.

Salicylates: acetylsalicylic acid (aspirin), sodium salicylate.

Fixed eruptions have been attributed to causes other than drugs. These have included colon bacillus vaccine, the drinking of wine and other alcoholic liquors, the inhalation of oil of Eucalyptus, psychic upsets, and menstruation.



Fig. 265.—Fixed drug dermatitis involving the abdomen. Avoidance of Midol and positively reacting foods resulted in about 90 per cent improvement. Discontinuance of dietary restrictions ten months later was followed by return of induration, ulceration, and necrosis.

Abramowitz and Noun point out that skin tests are of little value in diagnosis and conclude that a detailed history, the administration of a small dose of the suspected drug and the subsequent use of other drugs as controls are the best methods at hand for identifying the suspected agent.

The localized character of the eruption lends added credence to the concept that sensitization may occur in certain tissues of the body (shock tissues) without generalized sensitization, or that certain tissues may be more reactive than others even though sensitization is general. It has been shown by auto-transplants, in which the skin from the area of a fixed dermatitis has been transplanted elsewhere in the body, that the reactivity persists locally in the skin of the area even though transplanted.

The Commoner Drug Idiosyncrasies

Aspirin.—Although urticaria is the commonest symptom, this drug may cause angioneurotic edema, pruritus, scarlatinal erythema, conjunctival injection, conjunctival chemosis, coryza and asthma.

Prickman and Buchstein observed in a study of 62 cases of aspirin sensitization that asthma, urticaria, and angioneurotic edema are the commonest reactions. Other symptoms included vasomotor rhinitis, purpura and abdominal cramps. It is the one drug above all others which may be responsible for sudden anaphylactic death following a single dose.

Cooke has described violent asthma from ten grains of aspirin in nine different cases. In one-third of these urticaria was also present. In one a con-

stitutional reaction followed intracutaneous testing with 0.1 gram of aspirin. Positive skin reactions were observed only in those cases with history of urticaria.

Benson reports the death of an asthmatic woman, allergic to aspirin, who, when away from home, was given an aspirin tablet for relief. She died within two or three minutes. Deaths have been reported by Dysart, by Lawson and Thomas and by Francis, Ghent and Bullen. The case described by the last group is especially interesting. The patient had severe asthma at the time of aspirin medication. Thirty minutes later he went into collapse. With supportive treatment, epinephrine, caffeine and oxygen he was brought out of collapse and his blood pressure which had been unreadable rose to 160/120, but he did not regain consciousness and died thirty hours later. This experience indicates that death may occur late after a constitutional reaction and was probably due to a summation effect from aspirin shock plus his pre-existing severe asthma.

Shookhoff and Lieberman have described three cases with typical anginoid symptoms following aspirin ingestion. They were all middle aged, ranging from 35 to 44. Anginal attacks followed aspirin ingestion in from one-half to three and one-half hours. Attacks lasted rather longer than with ordinary angina and were accompanied by fall in blood pressure and collapse. In this way they simulated coronary thrombosis but presented no subsequent changes indicative of the latter. In one, electrocardiographic changes were observed during an attack.

Vaughan and Pipes have reported three cases of aspirin allergy. The first was a man aged 55. Merely touching the lips with aspirin would result in cyanosis and asthma within thirty seconds. This was followed by headache. On one occasion he had an ordinary headache and a friend gave him a powder which, unknown to him, contained aspirin. This resulted in a severe reaction lasting five hours and requiring several doses of epinephrine.

The second was a man in his fourth decade who had had a tonsillectomy. Powdered aspirin was applied in the tonsillar fossae. This was promptly followed by intense dyspnea and cyanosis and as is so often the case with constitutional reactions the patient became extremely apprehensive, crying out, "My God, what did they give me?" Cyanosis was a prominent symptom. The patient recovered after epinephrine therapy.

The third was one in which five grains of aspirin promptly produced shock, collapse and cyanosis without concomitant urticaria or asthma. He recovered following epinephrine therapy. He had had aspirin previously but never with severe symptoms.

This by no means exhausts the literature of aspirin allergy. Phillips has reported the case of an asthmatic who observed that his attacks followed the drinking of water from a certain well. This was pure well water, not chlorinated, and suspicion fell upon the lubricating oil used in the pump. The patient was allergic to aspirin, a coal tar derivative, and the question arose as to whether there was a relationship between aspirin allergy and possible sensitization to the oil.

Duke has stated that allergy may exist to impurities in the drugs rather than to the drugs themselves. One patient apparently sensitized to aspirin had difficulties from only one of five different brands. This one brand invariably produced abdominal colic.

Van Leeuwen has stated that in Holland 10 per cent of asthmatic patients are sensitized to aspirin. Unfortunately aspirin sensitization cannot be consistently demonstrated by skin test. As with most other drugs, no constant skin reactions are obtained. Duke suggests a method of testing which appears to be logical and which he states is safe. Aspirin, being soluble in slightly alkaline solution, is readily dissolved in the saliva. A very minute amount of an aspirin tablet is pinched off. The patient places this in his mouth and rolls it around his tongue. If he is strongly allergic, symptoms will come on as quickly as within 60 seconds. They are the usual symptoms, coughing, asthma, itching, etc. Further absorption of the drug can be promptly terminated by having the patient rinse the mouth with a very weak acid solution such as that made with a teaspoonful of vinegar to a glass of water.

Quinine.—This, another frequent cause of drug allergy, may produce urticaria, angioneurotic edema, vesiculation, desquamation, thrombocytopenic purpura, gastrointestinal symptoms, fever, coryza and asthma. Sensitization is so specific that one who is allergic to quinine may fail to have symptoms from quinidine. This is one of the few drug allergies in which successful desensitization has been reported following oral administration of minute amounts, with gradual increase. Quinine has caused allergic reaction following colonic absorption and may be responsible for contact allergy. Like acetylsalicylic acid, it is often present in proprietary preparations. Settle has described recurrence of dermatitis of the palms of the hands with bulla formation, somewhat resembling pemphigus, due to sensitization to quinine in a proprietary preparation (anaein). This contains aspirin, phenacetin, caffeine and quinine. The recurrent eruption in the same location appeared to be a fixed drug dermatitis.

The arsphenamines.—Untoward responses to injections with the arsphenamines include: the nitritoid crises, urticarial, morbilliform and scarlatiniform rashes, fixed skin eruptions, purpuras, acute yellow atrophy of the liver, leukopenia and granulopenia, encephalitis hemorrhagica and weeping and exfoliating dermatitis. Although it has been by no means demonstrated that all of these are allergic responses, there has been suggestive evidence in all and quite convincing evidence in many. Landsteiner and Jacobs (1936) have sensitized guinea pigs to arsphenamine and produced anaphylactic death from subsequent intravenous administration. Sulzberger and Simon point out that certain lots which have been shown by animal test to be no more toxic than others are more likely to produce these complications and they consider them more highly potential sensitizers. This may be true of batches coming from the same supply source. The cause is unknown.

These authors point out that arsphenamine sensitization is not synonymous with arsenic sensitization. The two differ clinically. In dermatitis due to the former there is no tendency toward subsequent keratosis and precancerosis. In the former sensitization appears to be toward the arsenobenzol complex, an organic arsenic compound, rather than to inorganic arsenic.

Patients allergic to arsphenamine, a trivalent organic arsenical, can often tolerate a pentavalent organic arsenical such as tryparsamide or an inorganic arsenical such as Fowler's solution. Occasionally the sensitization is even more closely specific, since Wechsellaum has reported an instance of salvar-

san sensitization in which neosalvarsan was taken without difficulty. On the other hand Robinson has shown tryparsamide to be potentially allergenic and Pillsbury has reported that occasionally one who is allergic to one arsenical will react to several or to all others. Ellis (1938) has described allergic dermatitis from tryparsamide. Frier and Sulzberger (1938) find that old-arsphenamine sensitization in animals results in simultaneous sensitization to at least two brands of neoarsphenamine (Abbott and Hoechst).

Gelfand has reported contact dermatitis from potassium arsenate, a constituent of Liquid Arvon, a hair tonic.

The symptoms of sensitization to organic arsenic compounds have been listed above. The most characteristic and at the same time most dreaded are exfoliative dermatitis and acute hepatitis, but other and more characteristically allergic skin responses may occur, as listed, as well as symptoms originating in internal organs. Purpura hemorrhagica deserves further mention since there is increasing evidence of its occasional allergic origin. Such cases due to arsphenamine sensitization have been described by Hudson and Falconer.

One type of eruption described by Milian, termed "the erythema of the ninth day," is not necessarily of serious significance. It is a measles-like or scarlatiniform eruption occurring about nine days after first injection and not appearing after subsequent injections. Milian attributed the eruption to the activation of a dormant infectious agent while Sulzberger inclined to its interpretation as a drug eruption.

Diagnosis of arsphenamine sensitization.—In the course of therapy with the arsphenamines it is most important that one be as constantly on the alert for early evidence of sensitization as one should be for evidence of stomatitis during mercurial treatment. The patient should be trained to report any unusual symptom, especially any skin manifestation that may have appeared subsequent to the last preceding treatment. The physician will do well to inquire concerning this prior to each successive injection. Even so, difficulties may be encountered since the person who becomes sensitized to the arsphenamines may also be sensitized to other allergens responsible for symptoms. A woman in the writer's experience had been receiving neoarsphenamine for a fusospirillary bronchitis. She was food-allergic and had had urticaria from various foods. She mentioned her skin symptoms to the physician who, however, felt that the dermatitis was due to foods and persisted in arsenical therapy. After two more injections she developed an acute exfoliative dermatitis with jaundice. Passive transfer studies enabled us to determine the offending foods and other allergens. Treatment in this case included specific dietary avoidance, in an effort to lessen the allergenic overload and promote a return to allergic balance. Two episodes during her recovery are of interest. She was allergic to beef. The hypodermic administration of Armour's peptone and decholin by mouth on different occasions caused recrudescence of skin symptoms.

Aside from constant watchfulness for the onset of toxic symptoms there is no reliable diagnostic measure. Neither scratch nor endermal testing nor patch testing has been found to be consistently reliable.

Cannon and Karelitz have carried out intracutaneous studies with arsphenamine in 209 syphilitics and 34 persons with other skin diseases. Im-

mediate traumatic reactions appeared regularly; these however persisted only 1 or 2 hours. What the authors termed positive reactions appeared in from 24 hours to several weeks after the tests had been made. They were observed in 84 patients but the authors found no constant relationship between the reactions and the clinical response to arsphenamine therapy. Positive reactions were observed in 48.7 per cent of those who had had arsphenamine dermatitis. This was a higher percentage than in any other major group but not sufficiently high for practicable purposes. The test appeared to lack specificity and was therefore adjudged of no diagnostic value. It was even positive in some patients presenting eruptions from medication other than arsenic, who had never received arsphenamine. Again, it was repeatedly negative in patients known to have complications due to arsphenamine. Some patients undergoing antiluetic treatment in whom the reaction was consistently negative developed arsphenamine intolerance. Other patients with positive reactions were able to continue arsphenamine therapy with no subsequent evidence of intolerance.

Robinson made patch tests on 165 individuals (22 normals; 54 syphilitics who had received or were receiving arsphenamine without reaction; 18 previously treated who had developed postarsphenamine jaundice; and 71 who had previous postarsphenamine dermatitis).

He found the patch test to be of no practical value for the demonstration of arsphenamine sensitization. It was sometimes positive in normal persons, and often negative in those known allergic to arsphenamine. Patients with positive patch tests often continued arsphenamine without developing trouble. The continuance or interruption of treatment could not be predicated upon the character of the contact reaction nor could one determine from this test whether a person who had had an arsphenamine dermatitis could safely re-inaugurate treatment. The only positive conclusion which Robinson was able to draw from his study was that, in a patient known allergic to arsphenamine, a positive patch test with neoarsphenamine is confirmatory evidence of persistence of sensitization.

Robinson has studied the leukocyte response following neoarsphenamine injection and has found that in those not sensitized the white count does not drop more than 1,000. In those who are sensitized there is a drop of more than 1,000. Two patients without evidence of arsphenamine allergy did show drops of more than 1,000 but after an early subsequent treatment they too developed arsphenamine dermatitis.

This author recommends an intravenous test in individuals who have had arsphenamine poisoning, to determine whether they may resume treatment. Three months should elapse following complete healing of the dermatitis. The patient is then patch tested with several preparations. He is next tested intravenously with a different arsphenamine from the one which caused trouble and one which gives a negative or at most borderline patch test. The initial intravenous dose is 0.025 gm. of arsphenamine, neoarsphenamine or silver arsphenamine or 0.005 gm. mapharsen. If this small dose produces itching no further injections are given. If not, the dose is gradually increased to the optimal therapeutic dose, injections being given at intervals of several days. It should be noted that this test is not for beginning sensitization, but for the recommencement of treatment when desirable after sensitization has been shown to exist.

Treatment of arsphenamine allergy. British Anti-Lewisite, or BAL as it is commonly called, is now the treatment par excellence for arsenical poisoning. It is 2,3-dimercaptopropanol, and was developed by the British to counteract the arsenical war gases. It has been shown to be of great value in the treatment of arsenic and mercury poisoning.

Arsenic produces its toxic effect by combining with $-SH$ groups in the cells. BAL has a greater affinity for arsenic than have the $-SH$ groups, and will combine with arsenic in the circulation or even remove it from combination with the $-SH$ groups in the tissue cells. The arsenic is excreted in the urine and may be found in greatly increased amounts after the use of BAL.

(Carleton (1946), Longcope (1946), Eagle (1946), and Sulzberger and Baer (1947) have presented evidence of the great value of the drug in arsenical dermatitis as well as other evidences of arsenic poisoning.

Functional pathology. Exfoliative dermatitis may occur as an allergic manifestation, more especially to metals and chemicals such as arsphenamine. In this connection it is interesting to note the usual cause of death from this disease. As a rule death is considered to be due to bronchopneumonia. Poole and Wehger suggest another cause. They report four deaths which clinically might well have been interpreted as from bronchopneumonia but where at autopsy the respiratory mucosa had undergone epithelial exfoliation equally as extensive as that of the skin. There was no bronchopneumonia. They suggest that the cause of death is obstruction of the air passages due to exfoliation of the epithelium. They find in the literature that of 14 autopsied deaths from exfoliative dermatitis 5 showed desquamation of the epithelium of the tracheobronchial wall.

Stokes and Cathcart found that symptoms of arsphenamine intoxication were not dependent upon arsenic retention in the body. The evidence therefore favors sensitization. They have observed cases with mild arsenical dermatitis in which there was a rapid extension, even with fatal results, following the stirring up of a focus of infection. Also removal of such a focus has at times resulted in rapid amelioration of the dermatitis. Their findings suggest a correlated bacterial factor which in their experience also includes the dermatophytoses. Arsphenamine dermatitis will not infrequently cause a flare-up of a relatively inactive dermatophytosis. They suggest that the dermatophytic focus may conceivably serve as a starting point in an arsenical dermatitis. They emphasize the desirability of careful watch for both types of dermatitis and appropriate treatment for each.

Sensitization to gold compounds. This is by no means common but is mentioned because of its similarity to sensitization to compounds of arsenic, another metal. Reactions have occurred chiefly in the course of gold treatment of tuberculosis and in dermatologic practice. Exfoliative dermatitis is a characteristic symptom. Here as in the arsphenamines, urinalysis shows no correlation between sensitization and renal injury.

Lichtenstein finds that among those treated with gold compounds complications occur only in persons who have developed a positive patch reaction. Symptoms include exfoliative dermatitis, neuritis and gastrointestinal responses. About 50 per cent develop evidence of sensitization. Lichtenstein reports that patch tests, performed at weekly intervals, usually became positive before complications occurred. Reactions were less frequent with gold

succinimide than with other gold compounds. Not all patients showing a positive patch test developed symptoms. Hudson has described purpura hemorrhagica following gold therapy.

Aminopyrine (amidopyrine). Credit must be divided among several individuals for the evidence that agranulocytic angina or primary granulocytopenia is probably a manifestation of allergic reaction to aminopyrine. Schilling (1929) suggested that "since similar pictures may be obtained experimentally in anaphylaxis, an anaphylactic condition instead of an individual disease is possible." Pepper suggested the possibility of an allergic reaction in 1931. These were but suggestions with no attempts at proof. The first serious study was by Kracke who called attention to the frequency with which persons with neutropenia had taken therapeutic doses of aminopyrine. His experimental work suggested that the benzene ring in this and similar drugs might be the poisonous factor. Madison and Squier appear to have first demonstrated that the factor suggested by Kracke was a factor because of specific sensitization. These authors showed that aminopyrine alone or in combination with other drugs is nearly always taken before onset of neutropenia. They pointed out that most persons take the drug in comparable amounts without symptoms. They produced positive patch reactions in convalescents from neutropenia by the application of aminopyrine to the skin and observed pronounced fall in white count coincident with the positive contact reaction. They produced an abrupt drop in granulocytes followed by death, in one rabbit fed on allonal, a compound containing aminopyrine. Seventeen other rabbits failed to show this response. This may be taken as evidence of allergy in one of 18 rabbits.

Many writers have confirmed the observations of Madison and Squier. Benjamin and Biederman reproduced a state of granulopenia within 48 hours after readministration of aminopyrine to a patient convalescent from the disease. Johnson observed recurrences of the disease on two occasions in a woman who took aminopyrine for relief of dysmenorrhea. Subsequent menstrual periods after discontinuance of the drug were not accompanied by neutropenia.

Other allergic reactions to aminopyrine include joint and pleural effusion, angioneurotic edema of the lips, papular erythema of the skin, urticaria, pruritus, erythema, rhinitis, conjunctivitis, dyspnea and collapse.

Novaldin.—Novaldin, sodium phenyldimethylpyrazolon, methylamino-methane sulfonate, is chemically related to aminopyrine and supposedly less toxic. Benjamin and Biederman (1936) tested a patient who had had agranulocytic leukopenia from aminopyrine, with novaldin (10 grains). This caused a drop in white count from 5,300 to 2,800 with a drop in polymorphonuclears from 69 per cent to 46 per cent. Endermal tests, patch tests and passive transfer with novaldin were negative.

Klumpp, reporting another case of novaldin allergy with agranulocytosis, brings out the point that this drug is not only a derivative of aminopyrine but contains the same chemical radicle which presumably causes agranulocytosis.

Sulfanilamide.—Sulfanilamide was introduced in this country by Long and Bliss (1937) for the treatment of beta hemolytic streptococcus infections. Since then its use has been extended to the treatment of erysipelas, pyelitis, meningococcus meningitis, gas bacillus infection, type 3 pneumococcus pneu

monia, brucellosis, gonococcus infection, and influenza bacillus infection of the urinary tract. It is being used experimentally in other infections. While the majority tolerate this drug without untoward effect, a number of reactions have been described, some of which are undoubtedly allergic in nature. These include maculopapular rash with pruritus, scarlatiniform eruptions, sneezing, asthma, urticaria, purpura and granulocytopenia. Fever frequently accompanies the reaction as is so often the case in other forms of drug allergy. The acute hemolytic anemia, toxic optic neuritis and photosensitizations that have been described are not as clearly allergic.

The various sulfonamide derivatives share in the ability to sensitize. Succinylsulfathiazole is absorbed very slightly from the gastrointestinal tract, and consequently causes little sensitization. Sulfathiazole and sulfadiazine are used quite indiscriminately, and are the cause of many allergic reactions.

Accumulated evidence justifies the statement that reactions do not occur at the first use of the drug. An incubation period is required. This is true both of the drugs given orally and those applied locally. Those who react from the oral use of the drug are those who have had it administered previously and there has been a period during which the drug was not given. Those developing skin eruptions following dermal application show a period of nine or ten days before the development of the skin eruption.

Fever is the most frequent symptom following oral use of the drug. Urticaria is frequent. Dermal application is frequently followed by a generalized eruption. It should be kept in mind that these drugs act as photosensitizers, and exposure to sun may greatly increase the intensity of the skin reaction.

A sulfonamide urticaria may persist for weeks after discontinuance of the drug, and may be quite resistant to all forms of medication.

Cinchophen. Cinchophen was introduced as a remedy about 1908. At that time it was called atophan. It is a remarkable drug in that it promotes the excretion of uric acid and is therefore quite specific in gout. It also has excellent analgesic properties, relieving pain quite as effectively as aspirin or aminopyrine. It consequently came into wide use in various forms of arthritis. Evidence was first brought forward in 1923 that cinchophen or one of its many derivatives may cause serious liver damage which is often fatal. By the end of 1930 at least 50 cases with 25 deaths had been reported. Not more than 1 or 2 per cent of those who take cinchophen or atophan over a long period appear to develop toxic symptoms. There is a record of a man with arthritis who took cinchophen daily for 18 years without trouble. On the other hand among those who are predisposed only a few doses may produce a fatal hepatitis.

Closely related derivatives include phenyleinchoninic acid, novatophan, atophenyl, diiodoatophan, biloptin, oxyl iodid, quinophan, agotan, neocinchophen, phenoquam, leucotropin, atophanurotropin, fantan, iriphan, tolysin, weldone, farastan, atoquinol, atochinol. This does not include patent medicines which may contain it.

Stieller has reported sensitization after three doses of cinchophen, with angioneurotic edema of the eyes, lips and vulva, general itching and tension of the skin. Sokolowski and Short and Bauer have reported cases of urticaria. Quick has suggested that the mechanism of the allergic liver lesion may be similar to that of the Arthus phenomenon.

Sulfur.—The parenteral administration of sulfur, usually in the form of colloidal sulfur, is said to be entirely free from hazard. Indeed it has been

stated that such large doses may be given that sulfur actually oozes out of the pores of the skin. However Tobias has reported one case of severe exfoliative dermatitis following a single injection of colloidal sulfur. A lady had had a chronic seborrheic dermatitis for which she had had many varieties of local treatment including sulfur, resorcinol and tar ointments, followed by x-ray treatment. Within twenty-four hours after the first intravenous injection of 2 cc. of colloidal sulfur a pompholyx-like eruption with considerable edema appeared on both hands. Within a week the entire skin surface was erythematous. This was followed by scaling, loss of nails and alopecia of scalp and eyebrows. The patient recovered slowly, over a period of eight months.

Although no answer is available, the question naturally arises whether the earlier sulfur inunction may have constituted the sensitizing dose and whether the previous x-ray treatment may have played a part. The local distribution of the original lesion contrasted with the generalized distribution of the subsequent dermatitis would appear to constitute an argument in the negative regarding the second question.

I have seen a young woman, allergic to horse serum, cheese and pineapple, who had been given a course of colloidal sulfur intravenously for arthritis. Four years later she was again started on the same treatment. After eight days she became acutely ill with generalized urticaria, fever, and angio-neurotic edema of the face and throat. She has received no more sulfur and one cannot therefore state categorically that this was the cause of the reaction. However none of the other known factors played a part, and in the ensuing eight months there has been no recurrence.

Barbiturates, luminal, amytal.—Luminal (phenylethylbarbiturate) has been in use for about twenty years. Cutaneous manifestations from idiosyncrasy to this drug were reported almost from the time of its introduction. Others of the barbiturates have been found occasionally responsible for drug allergy. The last added to the list is sodium amytal.

Langenback reports four cases in which after prolonged use of sodium amytal the drug was discontinued for periods of from eight to fourteen months. In each case immediately after resumption of the drug a characteristic macular rash appeared on the face and arms, usually with edema of the lips. The rash was followed by scaling. Langenback found that these persons, allergic to sodium amytal, experienced the same symptoms following plain amytal. However they could take luminal without discomfort. This is interesting as showing how an extremely slight change in the formula of a drug may alter its allergenic specificity. Sodium amytal (sodium isoamylethyl barbiturate) differs from the sodium salt of diethylbarbituric acid only in that an isoamyl group replaces one of the diethyl groups.

The characteristic dermatitis is morbilliform. Wile has reported two fatalities from luminal, with associated generalized morbilliform dermatitis.

Phenolphthalein. Phenolphthalein may be responsible for urticaria, erythema multiforme, or gastrointestinal symptoms, but the characteristic lesion is of the fixed dermatitis type. The problem of its recognition would be much simpler if it were not so widely used. It occurs in many proprietary laxatives. It may be responsible for the pink coloring of toothpastes, pink icing on cakes, and pink ice cream. For a time in certain cities of the Ohio River Valley it was incorporated in baker's bread which was sold as "prune

TABLE LXVII.—BELOTE AND WHITNEY'S LIST OF PREPARATIONS CONTAINING PHENOLPHTHALEIN

NAME OF PREPARATION*	FORM†	DISTRIBUTOR
Acet-aspirin compound	T	Drug Products Company
Agarol	L	Warner
Ago-cholan	T	Bilhuber
Allophen	T	Parke-Davis
Alipco	T	Drug Products Company
Allothal	T	Mallard
Allothalein	T	Abbott
Alphenine	T	Pitman-Moore
Analax	T	McKesson-Robbins
Aloin, cascarn compound	T	Massengill
Aphcopil [aloin and phenolphthalein compound]	T	American Pharmaceutical Company
A. S. A. laxative [contains acetylsalicylic acid]	T	Massengill
A. S. A. P. compound [phenacetin added]	T	Massengill
Baga	T	Towne-James
Bile salts combined	T	Lederle
Bile salts compound	T	Boericke-Runyon
Bile salts, holadin and phenolphthalein	T	Fairchild
Bile salts, sodium succinate and phenolphthalein	T	Fairchild
Bilox	T	McNeil
Biolax	T	Mallard
Bisalco	T	McNeil
Boals rolls	T	Boals Rolls
Blaud-copper compound	T	Massengill
Calomel and phenolphthalein [a common combination]	T	
Caroid and bile salts	T	American Ferment Company
Cas-ca-bile	T	Searle
Cascarets, chocolate	T	Sterling Products Company
Cascatone	T	Wyeth
Casophen	T	Davies-Rose
Castaloids	T	Merrell
Cathartones	T	Webster
Children's laxative candies	T	Carroll Dunham Smith
Chocolax	T	Stearns
Cholaphen	T	Stoddard
Cholatoi compound	C	Upjohn
Choleic	T	Merrell
Cholphenolate	T	Searle
Colactin	L	Spicer
Coco-lax wafers	T	Flint-Easton
Colalin with phenolphthalein	T	Schieffelin
Collosol kaolin with phenolphthalein	L	Crookes
Dioscorea compound	T	Massengill
Dublax	T	Schieffelin
Edema-aid, improved	T	Massengill
Ex-lax	T	Ex-Lax, Inc.
Fennamint gum	G	Health Products
Fenolets	T	Sharp-Dohme
Gall-ogogue	T	Westerfield
Hepatophen wafers	T	Drug Products Company
Hepatone	S	Sharp-Dohme
Homolax	T	Boericke-Tafel
Jayne's laxative pills	T	Jayne and Son
Kaylene-ol with phenolphthalein	L	Fougera
Kondremul with phenolphthalein	L	Patch
Laxa-phenolein	T	Van Dyke Chemical Company
Laxative syrup	L	Massengill
Laxocon with phenolphthalein	L	Schaefer-Pelps
Laxative pastilles	T	Chicago Pharmacal Company
Laxagen	T	Searle
Laxine	T	Columbus Pharmacal Company
Laxothalen	T	Pitman-Moore
Lax-thalein wafers	T	Standard Chemical Company
Liquid petrolatum with agar and phenolphthalein	L	Squibb
Liver tonic and laxative	T	Boericke-Tafel
Macarbo with phenolphthalein [magnesium carbonate compound with phenolphthalein]	T	McNeil
Manganese-ferronas compound	T	Drug Products Company
Mercolax wafers	T	Merrell
Mineral oil [liquid petrolatum] with phenolphthalein (colloidal emulsoid No. 9)	L	Drug Products Company
Neo-probilin	T	Shering-Glatz
Nuchol	T	Maltbie
Ovolax	T	Wyeth
Oxilets	T	Pitman-Moore
Oxiphen	T	Pitman-Moore
Petrolagar with phenolphthalein	T	Petrolagar Laboratories
Para-psyllium with phenolphthalein	L	Abbott
Petro-mul	L	Irwin-Neisler
Phenacetin compound	T	Massengill
Phenobilin	T	Norwich

*Material inserted in brackets is not part of the brand name but merely explanatory.

†C indicates that the preparation is in the form of capsules; G designates gum (chewing confection); L, liquids and emulsions; S, solids or salts; T, tablets, wafers, lozenges.

TABLE LXVII.—*Cont'd*

NAME OF PREPARATION	FORM	DISTRIBUTOR
Phenolphthalans -----	T	Keysall Chemical Company
Phenolphthalein compound [a common combination] -----	T	
Pheno-sagra -----	T	McNeil
Phenolphthalein-agar -----	S	Reinschild
Phenotab wafers -----	T	American Pharmaceutical Company
Phenopodoco -----	T	Drug Products Company
Phenolax -----	T	Upjohn
Phenotone -----	T	Korer
Pthalox -----	T	Sutliff-Case
Regulax -----	G	American Chewing Products
Rexall orderlies -----	T	United Drug Company
Rythmin -----	T	Carrick
Santonin, calomel and phenolphthalein -----	T	Massengill
Sodium oleate compound -----	T	Pitman-Moore
Sodium phosphate compound -----	T	Drug Products Company
Sodium and menthol compound -----	T	Drug Products Company
Taurocol -----	T	Plessner
Tauropfen -----	T	Drug Products Company
Tabalax -----	T	Kretschmar First Texas Chemical Manufacturing Company
Thaleocolate -----	T	Tailby-Nason
Thalettes -----	T	Mulford
Thalosen -----	T	Abbott
Triolax wafers -----	T	Mallard
Veracolate -----	T	Marcy
Zilatone -----	T	Drew

bread." It may be present in substances advertised as intestinal stimulants, intestinal antiseptics, adsorbants, stomachics, digestants, intestinal lubricants, and cholagogues. According to Belote and Whitney, it is used in materials advertised to the public for use in colds, grippe, rhinitis, coryza, disturbances of the liver and gall bladder, constipation and menstrual disorders. Even an aid to the reduction of edema appears in the list of substances containing phenolphthalein. These authors have listed 104 preparations which contain phenolphthalein. They emphasize that the list is by no means complete. It should be noted that the names of the preparations indicate a phenolphthalein content in only one-third of the series. Some state definitely that the preparation contains phenolphthalein. In many, the fact that phenolphthalein enters into the composition is hidden in the term "compound."

Penicillin.—Keefer and his associates (1943) reported a study of 500 patients treated with penicillin by various observers. Sixty-nine reactions were seen. These were chills and fever, urticaria, or even reactions quite like serum sickness. Lyons (1943) made a similar report. Since that time a large amount of literature has accumulated showing that reactions from penicillin are relatively common.

Reactions are more frequently characterized by urticaria and angioneurotic edema, but fever is not uncommon and other types of skin eruptions may occur. Some reactions are very severe and may appear identical with those seen in serum reactions. The symptoms may not appear for several days after the administration of the drug has been stopped, and may continue for many days. This is an interesting point when one remembers the rapidity with which penicillin disappears from the blood.

Since penicillium is a commonly distributed mold, it would be expected that some persons would be sensitized to penicillin by their exposure to the mold and that the first injection of penicillin might produce a reaction in an already sensitized person. Such reactions seem to be very rare.

Contact with penicillin may produce dermatitis. It has been found chiefly in physicians and nurses and is usually a dermatitis of contact type. Whealing has been reported as has edema of eyelids and conjunctivitis.

Toxic reactions may occur and should be distinguished from true allergic reactions. In the latter, Feinberg (1944) has found positive intradermal reactions; passive transfer tests may be positive (Crip, 1944), and Lamb (1945) reported finding precipitins. Heterophile antibodies were reported by Lyons (1943) which Cornia (1945) did not verify. Patch tests with crystalline penicillin have reacted positively (Pyle and Rattner, 1944).

Tyrothricin.—This antibiotic has come into use as a local agent. It cannot be used internally because of its hemolytic effect but is helpful in treatment of surface infections. Grolnick (1946) was unable to sensitize by patch tests the skin of any of 171 persons and reports of clinical sensitization have not been published.

Streptomycin.—This antibiotic has not been widely used in civilian practice to this date. Toxic symptoms have been reported; particularly those of involvement of the eighth nerve have been very disturbing. With increased use of this substance allergic reactions may be reported.

Thiamine hydrochloride.—The only reports of sensitivity to vitamins refer to thiamine. Some of these reactions followed intravenous and some followed subcutaneous injections. There had always been previous treatment with thiamine which probably sensitized the patient. Symptoms include rhinorrhea, urticaria, generalized itching, asthma and even cyanosis and collapse. Death has been reported.

Acacia.—Inasmuch as acacia is sometimes used intravenously in combating surgical shock, Maytum and Magath undertook studies to determine whether it would be possible to produce allergy thereto. In 19 animals, on reinjection, 4 showed mild anaphylactic symptoms; 3, severe symptoms; 2, very severe symptoms; and 3 died. This investigation was undertaken because a patient experienced mild anaphylactic symptoms, which responded to epinephrine following repeated infusion with acacia solution. They emphasized the need for caution when repeated injections must be given. Bohner (1941) reported ten printers with asthma from inhalation of gum acacia used in offset printing.

Narcotics.—Scheer and Keil reported (1934) that after careful review of the literature only 6 cases of allergy to *codeine* had been reported. They added a seventh. Codeine overdose will produce a rash usually distributed on the inner aspects of the arm, the flanks, abdomen and the inner sides of the thighs and knees. The allergic skin manifestation differs in that it appears following normal or small dosage and differs in character. It begins as a multifollicular eruption on the patient's neck, rapidly becoming intensely pruritic, scarlatini-form and involving the face and chest.

The case of Scheer and Keil reacted to a dose of one grain. Intracutaneous skin tests and passive transfer were valueless, since codeine like morphine is a naturally urticating substance which produces so-called positive reactions in all skins. They did, however, observe a positive patch reaction in this patient following the application of codeine phosphate and a negative patch in the same patient from morphine sulfate.

If this is to be taken as evidence of sensitization, it has added interest in the high specificity of the reaction since codeine differs from morphine only in the possession of a methyl group. For the patch test the drug must be in solution. Codeine phosphate solution, one grain to the ounce, was positive while codeine phosphate powder was negative.

Harris (1934) reports a case, typically scarlatiniform in type, which he attributed to codeine. This cleared up within 3 days after discontinuing codeine. The patient later gave positive scratch reaction to codeine solution (1 grain in 1 ounce of distilled water) while the control reaction was negative. The codeine reaction was very definite, with pseudopod formation. The patient could not be persuaded to make another trial of taking the drug. This may be recorded as a codeine rash, but the author should have carried his study farther, applying the same test to normal controls.

Local anesthetics.—Waldbott (1932) reports the case of a perennial asthmatic in whom on two successive occasions severe asthmatic paroxysms followed the application of *cocaine* crystals to the nasal mucosa. He reports sudden death following the application of *procaine* hydrochloride.

Iodine, iodized oil.—Allergy to iodine preparations is not new. It may be severe, even fatal. The source of contact is occasionally hard to trace. Iodized salt is an example. Waldbott mentions a patient with asthma associated with the eating of iodized salt. She reacted to various allergens but was not relieved until ordinary table salt was substituted for iodized salt. Subsequent trial of iodized salt caused return of symptoms. When one considers the rather widespread use of iodized oil intratracheally in the treatment of respiratory allergy, it is surprising that more cases of sensitization have not as yet been reported. The writer has been told of two unpublished cases, one with shock, and one with death, which he has not authenticated. Goldstein reports a fatal iododerma following the diagnostic use of iodized oil in the lung.

A woman of my acquaintance, allergic to iodine, found that she could not take laxative containing agar which is a seaweed product.

Other Allergenic Drugs

The preceding discussion in no way represents a review of the literature. Contributions are so numerous that space does not permit this. Most of the discussion deals therefore with the more recent observations. The following list of drugs to which idiosyncrasy has been reported is probably not complete. Apparently one may become sensitized to almost any drug which may be introduced into the body.

Acetanilid	Creosote	Mercurochrome	Procain
Allonal	Cubeb	Mercury	Pyramidon
Aminopyrine	Digitalis	Metaphen	Quinine
Antipyrine	Dilaudid	Methylsalicylate	Rhubarb
Argyrol	Dinitrophenol	Morphine	Salicylic acid
Arsenic	Dionin	Novocaine	Salol
Arsphenamines	Emetin	Opium	Sandalwood oil
Aspirin	Ephedrin	Pancreatin	Senna
Atabrine	Epinephrine	Pantopon	Sommacetin
Atophan	Ergot	Papain	Stramonium
Barbiturates	Ethyl urethane	Penicillin	Streptomycin
Belladonna	Evipal	Peptone	Sulfanilamide
Bismuth	Hyoscyamus	Phenacetin	Sulfonamides
Bromides	Insulin	Phenobarbital	Sulfur
Caroid	Iodides	Phenolphthalein	Thiamine
Chloral	Iodoform	Pituitary extract	Tincture of delphinium
Cinchophen	Ipecac	Polyphyllin	Turpentine
Codeine	Larodon	Pokeroot	Urease
Codliver oil	Luminal	Potassium chloroplatinate	Veronal
Copaiba	Lycopodium		

Diagnosis of Drug Allergy

As a rule there is no great difficulty in suspecting drug allergy in a given case. Proof is sometimes another matter. Since within recent years it has become evident that drug allergy may cause serious conditions such as acute hepatitis, exfoliative dermatitis, neutropenia, purpura, there should be less future difficulty in the recognition of new drug allergens. Experimental proof is not easy, since skin tests are not reliable, but relief of symptoms following avoidance may be looked upon as suggestive confirmatory evidence.

Often the patient will inform the physician that he has an idiosyncrasy to this or that drug. It is a foolhardy doctor who ignores this information and proceeds to administer the drug on the assumption that the patient is exercising his imagination. Allergists have frequent occasion, when listening to the patient's recitation of his experiences, to marvel at how many doctors belong in this category. Sometimes the patient is in error, but this cannot be presumed. Many will state that they cannot take aspirin but can take empirin or acetidine, both of which contain aspirin. The aspirin death described above was due to the fact that the patient who knew beforehand that he could not take aspirin forgot to tell the doctor until after he had swallowed the tablet.

There are drug allergies who have never suspected the etiologic agent. With them the interrogation must at times be most elementary before the possibility of drug idiosyncrasy is established. The patient, asked what drugs or medicines he takes, may promptly answer "none" even though he is taking a laxative each evening and a headache powder or aspirin several times weekly. A patient known to be allergic to atropine continued to have asthma and urticaria. We finally traced the cause to atropine in lapactic pills which were being taken daily as a laxative. Sulzberger has listed a series of interrogations designed to gain the necessary information. The list may be added to as needed.

1. Do you suffer from headaches? What do you take for them?
2. Have you ever taken aspirin, pyramidon, etc? How long ago did you last take it?
3. Do you sleep well? What do you take for sleeping?
4. How are your bowels? When irregular what do you take for them, ex-lax, agarol, etc.?
5. Do you feel well or run down? Do you take tonics, blood purifiers or herb teas?
6. Have you pain at the menses? Do you take pills or patent medicines for it?
7. Have you hang-overs and what do you do for them?
8. Do you have stomach upsets and what do you use against them?
9. When have you been to the doctor or the dentist last and for what? What did he prescribe?
10. Have you had any injections? What were they? Who gave them? What were they for?
11. How are your sinuses and what do you do for them?
12. Is the package of salt in your kitchen marked iodized?

It should be borne in mind that drugs with which one may come in daily contact are usually not thought of as medicines, phenolphthalein being an example. Quinine, resorcin, etc., may be used in suppositories. Ipecac is present in some tooth pastes.

The doctor should recall always that the names of the drugs, especially proprietary drugs, do not always indicate the ingredients.

There is no reliable diagnostic test for a suspected drug. Skin tests are more often negative than positive, even though the drug is allergenic. Those drugs which are simple plant extractives may give positive skin reactions

Aspirin and quinine have been found to give true positive reactions more often than the others. Serious reactions have followed endermal testing and scratch tests are therefore to be preferred. Certainly no drug should be tested endermally without preliminary scratch. Certain drugs, particularly those of the opium series, are, like histamine, naturally urticating. With them skin tests are therefore of no value. W. Jadassohn has found the histologic picture of wheals from the morphine series indistinguishable from that of histamine wheals. Eosinophiles were present in all. Sulzberger suggests that this may be interpreted as indicating that eosinophiles are not characteristic of an atopic or allergic reaction, but are simply pathognomonic of a wheal, or of any rapid exudative response.

As has been seen in the discussion of the arsphenamines and gold salts, patch tests may be positive but do not necessarily indicate trouble in the individual case. Conversely, patch tests may be negative in the presence of active allergy.

Passive transfer has rarely been reported positive with drugs and we may say that in general passive transfer is negative.

Duke has suggested a test for aspirin allergy based upon the observation that aspirin is insoluble in acid. This has been described above. Robinson's intravenous test for persistent arsphenamine sensitization has been described.

Treatment

The simplest treatment is the best, avoidance of the offending substance. Sometimes, as in the arsenicals, other drugs with similar action may be substituted. This is true among the analgesics and hypnotics, but the patient should understand that he may later develop sensitization to the substitute drug. Furthermore the new drug should be substituted only after careful trial with greatly reduced dose. If nonreactive, the size of the dose may be gradually increased.

Successful desensitization has been reported, especially with quinine. The same general principle is followed as in all other desensitization processes, gradual increases from an original minute dose. Heran and Saint Girons started with 5 mg. of quinine. The drug was given orally several times daily. At the end of one week one grain was being given daily.

For the relief of acute symptoms adrenalin, ephedrin and the synthetic ephedrins are usually temporarily efficacious. Purgation, diuresis and supportive therapy may be used as indicated.

The antihistaminic drugs, Benadryl and Pyribenzamine, are valuable additions to our therapy. They will usually relieve the urticarial type of eruption and control the itching of the eczematous eruptions. They do not relieve the eczema itself. They seldom control asthmatic paroxysms and fail often to control rhinorrhea. Rarely these drugs may cause an urticarial eruption.

Experimental Considerations

The early suggestion that drug idiosyncrasy might be a part of the picture of anaphylaxis, and its explanation in terms of haptens have been described. On the clinical side Cooke emphasized early (1919) that hypersensitiveness to drugs is probably allergic and should not be confused with exaggerated normal reactions to the same drug. Among 15 cases he found a positive family history of allergy in 12 while in the remaining 3 the patients themselves had obvious

allergy such as asthma, hay fever or urticaria. Clinically, therefore, drug sensitization appeared to fit into the allergic picture. Furthermore the symptoms were those found in the allergic group, not those of drug action.

Successful passive sensitization of animals using blood from human beings with drug idiosyncrasy has been reported by Bruck (antipyrine), Klausner (potassium iodide) and by Cruveilhier. Other investigators have failed to duplicate the results. Swift sensitized guinea pigs against a mixture of guinea pig serum and salvarsan and was able to desensitize with small preliminary doses. As far as they go these observations show a correspondence between clinical allergy and experimental drug anaphylaxis. Coke (1929) has reported successful passive transfer. While his patients did not give positive skin reactions to aspirin he found that if he himself took aspirin and then skin tested the patient with his own blood the reactions were positive.

It should be borne in mind that sensitization need not be to the entire drug but may be to certain radicles thereof. One person may be allergic to iodine. Another, allergic to iodoform, may not be sensitized to the entire drug nor to the iodine, but to the methyl radicle. Maloney has observed a woman who was allergic to any drug containing the phenyl group in its nucleus, such as aspirin, pyramidon, antipyrine, phenacetin, quinine, luminal, allonal.

CHAPTER LXVI

ALLERGY TO BIOLOGIC PRODUCTS

This might be classed as drug allergy were it not that the preparations used are animal derivatives, usually containing some amount of protein and that hapten activity is therefore not requisite. This is borne out by the fact that positive skin reactions and positive passive transfer are usually observed. Allergy has been reported to insulin, pituitary extract, thyroid, liver and pancreas extract. Even adrenalin has been incriminated, vasomotor rhinitis having been reported by Peshkin as due to the inhalation of epinephrine crystals.

At times the gland secretion itself is responsible, while at others sensitizations occur to the protein of the animal from which it is derived. Thus insulin allergy has been reported as due to crystallized insulin which is itself a protein, and to beef and pork. In some instances the menstruum is responsible, reactions having been attributed to the corn oil or peanut oil in which the estrogenic hormone is dissolved.

Insulin.—Jeanneret (1929) observed positive reactions to cow, hog, horse, and sheep insulin and successfully desensitized by repeated skin testing. Other early reports include those by Tuft (1928), Williams (1930), Grishaw (1931), Campbell, Gardiner and Scott (1930), Bryce (1933). Allan and Scherer (1932) reviewed the literature on the subject.

Davidson (1932) reported a case allergic not only to commercial beef insulin, but also to purified pork insulin. In 1935 he reported sensitization to crystalline insulin. Bernstein, Kirsner and Turner have reported successful anaphylactic sensitization of guinea pigs with commercial crystalline insulin.

J. H. Lewis sensitized guinea pigs with beef and pork insulin following which he demonstrated reaction to crystalline insulin by the Dale uterine strip technic, thus showing that sensitization in this case rested not on the protein of the animal of origin but upon the insulin molecule itself.

Williams (1933) reported the case of a woman who had been receiving insulin for six years without untoward effect, who then developed colonic hyperirritability with edema of the eyelids, which was traced to pork insulin. On changing to beef insulin the symptoms cleared up and remained relieved.

Murphy, Beardwood and Miller (1934) reported two cases, one with urticaria in whom the sensitization was shown to be to insulin itself, and the other with an asthmatic reaction (an individual obviously allergic and with a previous history of asthma), in whom the sensitization was moderate to insulin and more pronounced to pork. She tolerated beef insulin but the combination of two allergens, insulin and pork, promptly produced symptoms. These authors, like others, remark on the increased severity of the reaction, if insulin is given after a prolonged period of abstinence therefrom. Unsuccessful attempts were made to elicit passive transfer in the case reacting with urticaria. Successful passive transfer has been reported by Tuft, and by Campbell, Gardiner and Scott.

Criep (1941) reported two cases, Staffieri and Vila (1943) reported three sensitive to crystallized insulin, and many later reports are available. Baldwin (1947) estimates that among the diabetics at the New York Hospital about one of each thousand patients reacts to insulin. Some earlier reports showed higher figures. It is probable that improved methods of preparation have lowered the number of reactions.

Symptoms and physical findings. Reactions range from local irritation, urticaria, generalized urticaria, angioneurotic edema, asthma, nausea, vomiting, abdominal cramps to general prostration and circulatory collapse. Local urticaria is the most frequent symptom. Johnson has described a late pyrexia with acute joint symptoms resembling rheumatic fever, coming on two weeks after insulin discontinuance, which he suggests might be similar to serum sickness or drug fever (see sulfanilamide). No deaths have been reported.

Antigenic substance.—In many instances it may be shown that the patient is sensitive to crystalline insulin. In others the reaction is to the pancreatic tissue and may be a true organ specificity or it may be a sensitivity to pork pancreas, for example, and the patient can use beef insulin without reaction. In other words, some of these reactions are reactions to the purified endocrine substance, while others are sensitive to the tissue from which the product is made. This latter is not a true allergy to an endocrine product.

Evidence favoring allergy.—1. Modern methods of purification are such that after recrystallization a unit of insulin contains only about 0.001 mg. of nitrogen. However, as has been observed with pollen extracts, this represents sufficient protein to be of allergenic significance.

2. Reports in the literature indicate that at least 8 to 10 days are required after commencement of insulin medication before allergic reactions appear.

3. Passive transfer studies have been positive.

4. Positive skin tests, reagins and precipitins are usually demonstrable, and loss of clinical sensitivity is coincident with the disappearance of reagins.

5. These four observations constitute strong evidence that allergy is playing a part, especially when coupled with the fact that symptoms are allergic in nature.

6. Finally, Bernstein, Kirsner and Turner (1938) have successfully sensitized guinea pigs to both commercial and crystalline insulin, producing anaphylactic shock on reinjection.

Treatment.—Sensitization may occur to the protein of the animal from which the insulin is derived or to insulin itself, which according to most recent observations appears to be protein in nature. If the first is the case a change to another brand of insulin may suffice. The various insulin manufacturers can provide pure pork insulin or pure beef insulin for those allergic to beef or pork.

When sensitization exists to insulin itself, the problem is more complicated. Some who cannot take ordinary insulin find that they tolerate protamin insulin, or so-called "crystalline insulin" which appears to be a zinc-insulin combination. On the other hand, I have observed one diabetic who experienced urticaria from protamin insulin and "crystalline" insulin, but tolerated plain insulin.

If these procedures are ineffective, desensitization may be attempted. Such gradual desensitization is usually, though not always, successful. Collens, Lerner and Fialka desensitized two patients with commercial insulin starting with 0.0001 unit, and reaching a point at which both patients were able to tolerate as much as fifteen units twice daily. Desensitization lasted only for one month.

Spontaneous desensitization is probably more frequent than has been generally realized. It has been reported by several observers. As Cripie states, "Had so-called desensitization been attempted in Case 28 by repeated administration of small doses of tissue extract shortly after he developed the allergic reaction, his subsequent tolerance of tissue extract naturally would have been interpreted as being caused by this procedure and not by a spontaneous loss of sensitivity as the facts indicate."

Thyroid extract.—Rowe has described sensitization to thyroid extract derived from pork, in a woman who had been allergic to pork since childhood, which disappeared when beef thyroid was substituted.

I have observed a middle-aged woman who reacted with constant headache whenever she took thyroid extract, which was relieved on its avoidance. The administration of synthetic thyroxin caused prompt return of the headache which again was relieved following discontinuance. Sodium or potassium iodide caused no symptoms. Scratch reactions were negative to beef, veal, pork and lamb. Endermally, pork and lamb were borderline, while beef and veal were negative.

Pituitary extract.—Rowe has described extreme sensitization to pituitary extract with collapse and gastrointestinal symptoms. In a second case urticaria appeared when pituitary extract was recommended after a period of abstinence. It had previously been used over a period of eight months. A third case "developed severe asthma and collapse after the eighth injection of a pituitary-like hormone."

Simon and Ryder have demonstrated an organ-specific substance common to the pituitaries of different animals and of man, to which one may be sensitized.

The following case was described by Vaughan and Pipes.

A woman was known allergic to veal since childhood and had reacted by skin test to this protein. She also reacted to ragweed, June grass and orchard grass. For the treatment of menorrhagia she was given antuitrin S. She at once developed urticaria and cough, became cyanosed, and went into shock. The attending physician described the condition as "puffing up like a pouter pigeon." She was treated with adrenalin and recovered after four or five hours but urticaria persisted for four or five days.

Phillips (1942) reported a case of "allergic shock" from the injection of Synapoidin, a combination of gonadotropin from human pregnancy urine and extract of anterior pituitary. The patient developed a scarlatiniform eruption followed by massive urticaria. She then developed nausea, acute abdominal pain and collapse. Later an intradermal test was positive.

Epinephrine.—Deissler has described a case sensitized not only to therapeutic adrenalin but also to synthetic epinephrine. Balyeat and Rusten describe a case of urticaria allergic to epinephrine. However, this case is not clear-cut, since the urticaria attributable to epinephrine did not occur when foods to which the patient was allergic were eliminated.

Pancreatin and trypsin.—Rowe states that he has observed gastrointestinal reaction and migraine in a few patients who were sensitized to pork, after taking powdered pancreatin and trypsin by mouth.

Liver and liver extract.—Rowe, who has reviewed the literature on the subject of liver allergy, states that one may be sensitized to liver taken as a food, without having symptoms from the muscle food of the same animal.

It seems entirely possible that organ specificity of parenchymatous tissues may exist, comparable to organ or tissue specificity in the lens, feathers, hair, and eggs. In other words, liver may contain both beef protein and liver protein, the former being more specific for beef, the latter for any liver. Except for Crip's case mentioned below, I know of no work that has been done to establish this, but not infrequently one will observe a patient who eats beef with impunity but cannot take sweetbreads or kidney or possibly liver or brain. Rowe's patient could not eat beef or lamb liver but did tolerate chicken liver and the meat of beef and lamb without symptoms. Allan and Scherer have described sensitization to beef pancreas in the absence of sensitization to beef muscle.

Vaughan and Pipes described a reaction to liver extract. The patient had been taking liver by mouth. Two or three minutes after the first injection of liver extract, 1 cc. intramuscularly, the patient became cyanotic and pulseless. There was no urticaria nor asthma. Adrenalin treatment resulted in prompt recovery. Other patients had been given the same extract in the same way without ill effect. This may have been an allergic reaction or simple syncope.

The writer observed a patient who had received Chappel's liver extract subcutaneously twice weekly for three or four months and who at the first injection after a lapse of six weeks developed asthma and urticaria. The symptoms, though definite, were not severe and required no treatment. No further hypodermic medication was given but the patient subsequently ate veal liver without symptoms.

Crip (1938) found 6 reports of sensitization in the literature and added 1 of his own. Reactions included asthma, urticaria, angioneurotic edema and anaphylactic shock. Crip's patient also had urticaria from strawberries and gastrointestinal symptoms from apples, oranges and cabbage. He became allergic to liver extract after a year of parenteral administration. He reacted to liver extract from beef, lamb, chicken and hog but not to serum or muscle extract from these animals. This appears to have been a clear-cut case of organ specificity rather than species specificity. Both direct and indirect testing were positive. Following avoidance, sensitization disappeared at the same time that reagins disappeared from the blood.

Since Crip's report there have been two others. Krantz described systemic allergic reaction after repeated liver extract injections. This patient reacted to horse meat and Krantz suggests that the liver extract may have been derived in part from horse liver. Gardner described a case which he interprets as allergic reaction to the oral administration of liver concentrate. The patient was allergic to strawberries and ragweed. Following oral administration of Iextron, Jeculin or extralin, all preparations containing liver extract, she reacted regularly with severe weakness, dizziness, palpitation, and menorrhagia. No tests were made. Discontinuance of medication was followed by recovery. The administration of other constituents of these preparations, especially iron preparations, caused no such symptoms.

Kaufman, Farmer and Reich (1943) reviewed the literature and found 50 cases reported to which they added eleven. They found the make of extract and the dose to have little relation to the reaction. Reactions usually occurred after several well-tolerated injections and then, they found, that injections might be continued with the same extract and, in many instances, no other reactions occurred. The clinical manifestations were quite varied. They believe that the reaction is not due to histamine but is on a true allergic basis.

In such cases, when liver therapy must be continued, if sensitization is species-specific rather than organ specific, substitutions may be tried. Liver extract—Lilly is prepared exclusively from swine. Liver extract—Chappel is said to be prepared exclusively from horse liver.

Ovarian hormone. A number of reports have appeared indicating allergic reactions to ovarian hormone injections may be fairly frequent. In many instances it has been shown that the reaction is to the menstruum and not to the hormone itself. Corn, peanut, or other oil may be responsible for the reaction and change to a product in another menstruum may be all that is indicated. Zondek, Bernhard, and Bromberg (1945) found women showing various conditions associated with menstrual or menopausal disturbances showed reagins to the steroid hormones. They believe this is evidence of allergy to endogenous hormones.

Diagnosis and Treatment

As in drug allergy, the first step toward diagnosis consists in an awareness of the fact that a patient receiving an endocrine product may become sensitized thereto, and the suspicion that allergic symptoms developing during treatment and, more particularly, if there has been an interim without treatment, may be due to some constituent of the medication.

Skin testing may be of diagnostic value although a negative reaction is not as significant as a positive. Sensitization having been proved, effort should be made to determine whether allergy is to the hormone itself or to the protein of the animal from which it is derived. In the latter case substitution from some other animal source may be effective.

If sensitization exists to the actual hormone and continued treatment is clearly indicated, desensitization may be tried.

PART XIII

CONTACT ALLERGY

The poisonous weed, being in shape but little different from our English yvie; but being touched causeth redness, itching, and lastly blysters, the which howsoever, after a while they passe awaye of themselves without further harme; yet because for the time they are somewhat painefull, and in aspect dangerous, it hath gotten itselpe an ill name, although questionlesse of noe very ill nature.

—CAPTAIN JOHN SMITH

CHAPTER LXVII

CONTACT ALLERGY TO PLANT AND ANIMAL PRODUCTS

Definitions.—There has been much discussion concerning the appropriate use of the terms “eczema” and “dermatitis.” European dermatologists have used eczema in the same significance in which more recently we use the term contact dermatitis. Willan (1800) described eczema as a “condition generally due to the effects of irritation whether externally or internally applied and occasionally produced by a great variety of irritants in persons whose skin is constitutionally very irritable.” At that time physicians probably felt that they had a fairly clear idea of eczema. Undoubtedly the term comprised a multitude of skin manifestations. From the commencement of modern dermatology, around 1850, to the present, one dermatosis after another has been segregated from the group of eczemas, until today we may look upon Sutton’s description as being as good a definition as any: “It is a sort of dermatological scrap heap from which, from time to time, some newly assembled group of symptoms is being removed as a distinct clinical entity.” This being the case, the term *eczema* is better avoided in a condition as clear cut as *contact dermatitis*.

The term *dermatitis venenata* has been employed in a similar significance. In America we have come to think of it more as applying to contact dermatitis caused by so-called poisonous plants such as poison ivy, oak and sumac. However, the term carries no such connotation, indicating only dermatitis due to the action of some poison. It may be and has been applied equally well to dermatitis due to the irritant action of drugs and chemicals. But it carries with it the idea of an intrinsically poisonous agent and is therefore not quite appropriate in allergy. The discussion therefore finally resolves itself into a choice between “contact dermatitis” and “contact allergy,” as the more appropriate term. There are valid arguments for and against each.

Evidence of an allergic factor. Those who doubt a basic identity between anaphylaxis and contact dermatitis stress the absence of anaphylactic anti-

bodies; the absence of reagins, as demonstrated by failure of passive transfer; the absence of evidence of sensitization of internal structures, reaction being obtained in the skin alone; and the fact that heredity appears to play no part.

It is quite true that the evidence indicates that nearly all persons may be made to react to contact allergens, but this does not indicate a basic difference. While all may be made contact reactive experimentally, most do not become so in the course of actual exposure. Furthermore, a high incidence of contact sensitization has been demonstrated only with a few contact allergens. An equally high incidence has been demonstrated with a few atopic allergens such as guinea pig or rabbit serum, horse serum and ascaris.

Since the demonstration of tissue antibodies, the presence or absence of circulating antibodies no longer assumes the importance that it did. Evidence of local sensitization in shock tissues in contrast to general sensitization makes the absence of systemic sensitization in contact dermatitis appear less important.

To the writer the important facts are: that a particular skin is originally nonreactive to a substance which is ordinarily not poisonous; that direct contact with this substance must be established; that this first contact does not cause reaction; that there is a definite incubation period after which the skin does react in an abnormal way and continues to do so after repeated contact, for a more or less indefinite time; and that this abnormally reacting skin can be shown to be different from other so-called normal skin. The basic allergic requisites are thus fulfilled. The experimental evidence substantiating these points will be brought out chiefly in the discussion of rhus dermatitis.

Evidence of an originally nonreactive skin. Spain (1922) observed that although 65 per cent of persons over 35 years of age react to the active principle of poison ivy, evidence of such sensitization was not found in 18 infants under eighteen months, similarly studied. Coca found only one susceptible among 12 children five years old or younger. This was a boy of five. Strauss tested 119 newborn infants ranging from one to four days old and found none to be allergic to poison ivy paste applied as a patch.

Although the North American Indian and adult whites have been found susceptible to ivy poisoning in approximately the same percentage (Indians, 56 per cent; whites, 58.8 per cent), the Eskimos of Baffin Land and, apparently the same race as the American Indian, did not react positively to test. Poison ivy does not exist on Baffin Land.

Evidence such as this strongly suggests that we are born without susceptibility to ivy poisoning and that its acquisition depends on postnatal exposure and contact.

Evidence that an insusceptible person may be made susceptible by contact exposure.—Strauss (1930) reported sensitization of newborn infants to poison ivy by means of cutaneous application in the form of a patch test, and by combined ingestion and cutaneous application. The skin sensitization was general, not localized to the area at which the extract was applied. In a later communication, 1934, he reported that feeding the extract alone did not produce cutaneous sensitization. Subcutaneous injection did not produce sensitization, only one of ten infants so treated becoming sensitized. In this instance there may have been some degree of simultaneous cutaneous applica-

tion. Cutaneous application with an ivy paste sensitized 72.9 per cent of 48 infants, sensitization persisting thereafter at least for about 20 months.

Artificial sensitization to ivy produced sensitization also to poison sumac. Straus concludes that the active principle in ivy and sumac is immunologically identical.

Evidence of an incubation period. Nestler (1904) who appears not to have been previously affected by primrose rubbed the unbroken skin of the left forearm repeatedly with the leaves and stalk of the plant. Not until 14 days after the beginning of his experiment did he observe evidence of a dermatitis. Low (1921) who had had no previous sensitization to primula (primrose) rubbed the juice upon his arm. There was no reaction. Three weeks later he repeated the experiment. After eight hours he developed the characteristic local dermatitis. He then exposed his brother who was also non-susceptible in the same way, but with skin rubbing approximately once each day for nine days. There was no reaction. Three weeks later he again exposed the skin. Four days after this renewed contact his brother's skin reacted with dermatitis venenata.

Field and Sulzberger, using the former as subject, since he had lived in Europe and had not been exposed to poison ivy, produced sensitization in much the same way and established the incubation period as ten days. These findings correspond surprisingly with the incubation period in other forms of allergy.

Evidence of an altered type of skin reactivity. Bloch transplanted skin from a patient with iodoform dermatitis to another with a healing burn. He also transplanted some of his own skin, not reactive to iodoform. After the graft had taken he dusted the areas with iodoform. A marked reaction resulted, limited to the section of skin obtained from the patient who was sensitized to iodoform. The patient's own skin and Bloch's graft failed to react. He repeated this experiment with a trichophytin-reactive skin (his own) and a negative control. The recipient, a patient with a chronic leg ulcer, was also nonreactive. After the graft had taken, he did skin tests with trichophytin on the patient's normal skin and on each of the two grafts. Positive reaction was observed only on his own graft. Although this latter is not a contact test phenomenon, it illustrates the point.

Evidence that the sensitization is local, not involving deeper structures.—Evidence of this is so abundant (absence of antibodies, negative scratch and endermal tests, absence of constitutional or other reactions following oral or hypodermic administration) that we shall limit ourselves here to the earliest observations. It should be noted parenthetically, however, that Landsteiner and Jacobs (1936) have produced anaphylactic shock on intravenous administration of chemicals which when applied to the skin produced a positive patch reaction.

Jadassohn found that iodoform caused no symptoms in cases of iodoform dermatitis when applied to the mucous membranes. Bloch found that in such cases even subcutaneous injection and internal administration as well as application to mucous membranes were ineffective.

Low has described the case of a woman whose skin was sensitized to iodoform and whose vagina was packed, following an operation, with iodoform gauze. She developed dermatitis of the vulva, groin, and lower abdomen but the vaginal mucosa remained unchanged even after twenty-four hours' contact.

It has long been thought that the same applied to the active principle of poison ivy, that it could be taken internally without symptoms. This is not altogether true. According to McNair, symptoms of poisoning, even death, may result, but even so, the most pronounced symptoms are cutaneous. He quotes the observations of Dakin over a century ago (1829) which showed clear evidence of greater susceptibility of the skin, even after the excitant had traversed the entire length of the intestinal tract:

"Some good meaning, mystical, marvelous physician, or favored ladies with knowledge inherent, say the bane will prove the best antidote, and hence advise the forbidden leaves to be eaten, both as a preventive and cure to the external disease. I have known the experiment tried, which resulted in an eruption, swelling, redness and intolerable itching, around the verge of the anus."

CONTACT DERMATITIS DUE TO PLANTS AND PLANT JUICES

The commonest of these is that to poison ivy, poison oak, primrose and Japanese or Chinese lacquer. This is an excellent point of departure in the discussion of contact dermatitis, (1) because it is one of the oldest manifestations, (2) it is clearly defined clinically, and (3) much of the experimental work which has led to a clearer understanding, has been done with these allergens.

Rhus Dermatitis

Primula.—Although primrose does not belong botanically in the rhus family, nor indeed in the rose family, it is included here because of the similarity of its effects and because while research in this country has dealt with rhus, similar research in Europe has been based on primula as the excitant.

The active crystalline substance, primine, has the composition $C_{14}H_{18}O_3$.

Rhus vernicifera.—Goldman and Pfosi write: "Lacquer eczema has been known for more than a thousand years; in the early days in China it was mistaken often for leprosy. In the second century B.C. crushed crab was prescribed as a specific for lacquer skin irritation and this remedy is used in China to the present day. Kampfer in 1812 described lacquer eczema in Europe. In 1887 Allan mentioned lacquer idiosyncrasy in natives and foreigners in Japan. In recent times attention has been called to this through contact with mahjong sets, and also from the use of earphones, of telephones and radios and even old vases." Japanese lacquer is obtained from the sap of *rhus vernicifera* (literally translated, the varnish bearing sumac). It is a small tree or shrub of the Orient.

The active substance, urushiol, is a catechol with an unsaturated side chain of the formula $C_6H_3(OH)_2C_{15}H_{27}$. The active principle in rhus toxicodendron appears to be identical.

Toxicodendron. Shelmire (1941) states that conservative botanists designate three species, namely, *Toxicodendron radicans*, *quercifolium*, and *diversilobum*. He cultivated several specimens of each of these species secured from various parts of the country. They were planted and cultivated under identical conditions. Since the variations on which difference in species is based were almost lost when cultivation was identical for all, he suggested that "this variable plant seems best treated taxonomically as a single pleomorphic species with several more or less consistent geographic variations." He states that poison

sumae belongs to the genus *Toxicodendron* and not to the genus *Rhus*, and should be designated as *Toxicodendron vernix* rather than *Rhus vernix* or *Rhus venenata*.

Mode of contact.—Some persons are so exquisitely susceptible to ivy poisoning that they insist that if they but walk through the woods, near ivy, they will develop dermatitis even though they do not touch the plant at all. McNair has, however, concluded that contact with the sap of the plant must be established, that the allergen is not volatile. Contact may of course be indirect as on the skin or bodies of animals or insects, on tools or on clothing (Howell has shown that smoke will not carry the active material except as particles of the plant may be carried in the smoke). Low quotes White's description of a six-year-old boy who was extremely susceptible to ivy poisoning. Another boy had been employed to tear up the rhus plants in the neighborhood.



Fig. 266.—Primula. Primrose does not belong to the rose family but is in a family of its own, Primulaceae.

Under careful supervision he subsequently washed his hands in hot soapy water followed with vinegar. Several hours later he took the susceptible child to a pond to bathe. While there he held him up by the armpits and rubbed his back. Two or three days later the child developed deep ulcers under the armpits and on the back, with the appearance of a severe ivy poisoning. After an illness of three weeks the child died.

Sap.—The fresh sap emulsion is the only part of the plant which contains the excitant. Anthers, pollen, xylem, epidermis, cork cells, and trichomes are not antigenic unless contaminated with the sap. The plant is most poisonous when containing most sap and when the leaves and stem are more susceptible to injury. As a consequence there are more cases in the spring time; fewer when the sap is drying and the colors are appearing on the leaves; and fewest during the dormant period from November until February. Another factor which controls the frequency of cases is the opportunity for contact. More persons are in the woods in the spring and summer than at other times.

There is one form of rhus poisoning in which the agent is not as easily suspected or traced and in which symptoms are at times not as clear cut, namely lacquer dermatitis.



Fig. 267.—Poison ivy and oak. Specimens photographed in an oak bog show leaves with general shape more characteristic of oak than ivy. Lower right, however, shows ivy leaves growing on the same stem with "oak leaves." Upper left shows ivy berries, important in identification.

Japan lacquer is widely used in the Orient as a furniture lacquer. When completely dry it is relatively harmless. Lacquerers wear gloves when engaged in their trade. It is stated that lacquer 1,000 years old has been found to cause trouble. However, as a rule drying and oxidation lessen its toxicity. Pusey has described acute dermatitis following the handling of a cane coated with Japan lacquer. In 1923 tins for canning pineapple in Hawaii were being passed through a hot bath containing one part commercial lacquer, five parts gasoline. Handlers of these tins developed lacquer dermatitis.



Fig. 268.—True poison oak growing in California, as a tall bush.

A few years ago the United States experienced a wave of popularity of the Oriental game mahjong. The boxes of the mahjong sets, especially the more elaborate and costly ones, usually were finished with Japan lacquer and a number of cases of lacquer dermatitis resulted.

Not all lacquered material causes lacquer dermatitis. There are natural lacquers of which the above is an example and artificial or synthetic lacquers. Most lacquers in use in the United States today are in the latter group. However, so-called Japan boxes, etc., may represent the former group. Artificial lacquers usually contain nitrocellulose, often pyroxylin, and resin to add adhesiveness, gloss and hardness (rosin, shellac, dammar, kauri, copals,

sandarac, mastic and elemi). These are natural resins. Synthetic resins are also used such as ester gum, bakelite, lewisols, etc. Plasticizers are added to prevent cracking and peeling. These are usually oils such as castor oil, rape seed oil, linseed oil. Finally there are solvents which are volatile such as ethyl acetate, butyl acetate, toluol, ethyl alcohol, benzol, etc. Pigments are usually added. As has been emphasized by Goldman and Pfosi, there is so much variation in the constituents of both natural and synthetic lacquers, that any case of suspected lacquer dermatitis should be tested against the particular lacquer under suspicion.

These authors tested 61 cases of contact dermatitis and 98 noneczematous controls, by patch tests, with 1 per cent Japanese lacquer in pure benzol, and with so-called artificial lacquers, an oil lacquer, a polish lacquer and a varnish, all applied full strength. Other control tests with possible contact allergens were applied. In the group with contact dermatitis from various causes they found that 29 or nearly one-half reacted to Japanese lacquer while only 2 reacted to artificial lacquers. Among the controls 12 or approximately one-eighth reacted to Japanese lacquer while one reacted to artificial lacquer. No case reacting to artificial lacquer failed to react to Japanese lacquer also. Among the 29 positive dermatitis cases lacquer was the probable cause in 2 and a possible cause in an additional 8. It would have been of interest in this series to have known also concerning reaction to poison ivy extract, particularly with regard to possible crossed reactions among the lacquer positive cases.

The authors bring out the point that, as first suggested by Bloch, the contact dermatitis patient is likely to react to eczematogenic substances which are not related to each other, in a rather general nonspecific way. The dermatitis patients reacted four times more frequently to Japanese lacquer than the control cases. This might be interpreted as tantamount to a non-specific reaction. We shall have more to say later concerning possible group reactions.

Diagnosis of rhus dermatitis. This is usually easy, based upon location, character, acuteness and severity of the local lesion. As a rule there is a history of possible exposure to poison ivy or poison oak. The lesion commences on exposed areas, hands or face, or elsewhere if one has been sitting or lying in the woods. The time interval following exposure is usually a matter of hours, rarely days. Contact surfaces soon become pruritic and red. Vesiculation occurs early. Secondary lesions are apt to occur early on the ears, around the eyes and mouth and on the genitalia, transferred by contact with the hands. The acuteness of the reaction in a previously clear skin is most suggestive. However, it should be borne in mind that, even if there is a history of possible exposure, the inciting agent may have been some other contact substance.

Patch testing.—This may be done with a minute portion of the leaf, not more than one-eighth inch square, but it is preferable to use diluted extract, since the reaction to even such a small bit of leaf may be severe. Extracts of the leaves may be made in alcohol, ether or acetone. A very satisfactory procedure with rhus plants as well as with all other plants with which one may have occasion to test consists in extracting one part by weight of the leaves or other test substance in five parts of acetone, with frequent shaking.

for twenty-four hours or longer. The acetone extract is then evaporated down to from one-half to one-fifth the original volume and stored in tightly stoppered bottles appropriately labeled and dated. With this procedure one may gradually acquire a large series of test extracts. Therapeutic oil extract in serial dilutions, using sterile almond oil, corn oil or peanut oil, may be made from the acetone extract. Olive oil is rather more irritating, due to higher concentration of fatty acids. One drop of the original acetone extract may be used for patch testing. Usually twenty-four hours' application suffices, but the patient should understand that if the site becomes irritated sooner the patch should be removed, the site gently washed with strong soap such as Octagon soap and water, and a sterile protective gauze applied, until the doctor can read the test.



Fig. 269.—Ivy dermatitis involving the backs of the arms, especially left.

Keeney, Sunday, Gay, and Lynch stated that tests made with a 1:25 peanut oil dilution of an ether extract were accurate. Seventy per cent of those giving histories of ivy dermatitis gave positive reactions with this test, and 14 per cent of those with negative histories gave positive reactions. Shelmire (1941) states that oil extracts are far less antigenic than acetone or ether extracts of equal dilution. Ether extracts seem to be slightly less antigenic than those diluted with acetone.

Local treatment. The toxic glucoside was first identified in 1907. It was found that it could be precipitated in part by lead acetate. Most of the local remedies used since then have been based on this theory of precipitation. Potassium permanganate has been very popular as has ferrie chloride. Strong soap has been relied upon by many. Schwartz, Warren, and Goldman (1940) recommended a vanishing cream containing 10 per cent sodium perborate. Shelmire's experiments (1941) would serve to cast a great deal of doubt on the efficacy of any of these measures, since he found the active principle of the oleo-resin to be very stable under various conditions and almost impossible to remove

by any means after once on the skin. It would seem that the only safe practice would be to cover the skin, when possible, with some protective ointment before the expected contact. Anything else is of questionable value.

Specific treatment.—The prophylactic chewing of the ivy leaf is an old-time remedy which is not especially harmful since the toxic principle is not particularly irritating to mucous membranes. Unfortunately, however, some of it may be deposited around the mouth, causing severe rhus dermatitis and, when swallowed, may cause considerable gastric distress.

Strickler (1918) attempted the oral administration of a tincture in dosage of 15 to 30 minims by mouth.



Fig. 270.—Dermatitis venenata, very mild, involving dorsum of hands.

The next advance was the parenteral injection of an alcoholic extract which, however, was quite painful. Molitch and Poliakoff (1936) immunized 40 boys who were proved by patch test to be susceptible to ivy poisoning. They used a 1:50 alcoholic extract made according to the method of Spain and Cooke, ranging the dose from 1 cc. of 1:1,000 dilution to 1 cc. of 1:500. Injections were given weekly. No local or systemic reactions were observed aside from itching at the site of injection. During the twenty weeks of treatment, with normal exposure to poison ivy, none developed rhus dermatitis. They concluded that immunization lasts while the injections are being given, rarely longer than a year thereafter.

These same authors (1938) injected 50 boys prophylactically, giving 1 or 2 injections of commercial poison ivy extract in oil; 7 developed rhus dermatitis during the season; 39 controls not immunized all developed the disease. The entire series of 89 were known reactive as evidenced by a positive past history.

A distinct improvement was the change from an alcoholic extract to an extract in almond oil, which appears to be nontoxic and more potent than the alcohol extract and is painless when given deep hypodermically or intramuscularly.

Results of treatment.—There has been some divergence of opinion concerning the efficacy of the oil extracts. For relief of the attacks we have used it routinely in those cases too far advanced to respond to the local application of ferric chloride and have usually found it efficacious. An enthusiastic report is that of Gowen who finds the almond oil extract safe, simple and efficient. He finds that one injection given in the spring of the year will sometimes protect susceptible individuals for as long as a year. After several annual injections one may be immune for one year, occasionally longer without treatment.

Unfortunately it is rather difficult to determine the efficacy of treatment, since a positive patch test does not become negative under therapy and since the actuality of exposure after the institution of treatment is always problematic. Blank and Coca have observed parallel series equally exposed, one treated and one not treated. This was a group of civilian conservation corps workers engaged in mosquito control, clearing streams and swamp areas and necessarily exposed to extensive contact with poison ivy and poison sumac. The first group received four injections at weekly intervals, of 0.5 cc. of



Fig. 271.—Healing ivy dermatitis of the hands.

almond oil containing 10 per cent by volume of acetone and 0.1 per cent of solids extracted from poison ivy leaves with acetone and freed from chlorophyll. Group 2 received similar injections of an extract containing twelve times the amount of poison ivy solids (1 cc. of extract containing 0.66 per cent solid). Group 3 received no injections. The injections were prophylactic. Those who developed ivy dermatitis were then treated either with the stronger extract, the weaker extract or with almond oil containing no ivy extract.

Two-thirds of the untreated cases developed rhus dermatitis; 20 per cent of those treated with the weaker extract and only 7 per cent of those treated with the stronger were similarly affected. The 66.7 per cent incidence among

controls corresponds closely with the normal incidences among the population at large, described by Spain as 65 per cent and by Deibert, as 58.8 per cent. Blank and Coca reached no statistical conclusion concerning the value of the extract in the treatment of rhus dermatitis once it had occurred. Since the subjects were equally exposed to poison sumac they conclude that ivy extract also protects against sumac.

Sompayrac (1938) reports no benefit in phylactic treatment, once the eruption has commenced. In a control group of 14 not treated with ivy oil the average duration of the disease was 9 days. In a treated group of 9, the average duration was 11 days. Nor did he observe any definite improvement in pruritus, following desensitizing oil treatment.

Shelmire (1940) advocated prophylactic treatment using an extract diluted in corn oil and given orally. The initial dose is one drop of a 1:100 dilution. Doses are taken daily and one drop is added every three or four days until a dose of ten drops is reached. In order to avoid irritation of the lips or mouth, the drops are placed in ordinary gelatin capsules. The ten drop dose is continued until an ounce of the dilution has been used when a 1:50 extract is substituted. The initial dose is five drops and it is increased as before until a dose of ten drops is reached. If the patient is not too sensitive, a 1:25 solution is then used in the same manner. Shelmire does not believe that prophylactic treatment by injection is as satisfactory as the oral method, and he believes that phylactic treatment by either method is of little or no value.



Fig. 272.—Positive patch test to ivy extract (Rholigen). (Courtesy of Dr. A. H. W. Caulfeild.)

Preparation of extract.—

Shelmire's method. Mature, green plants are collected, placed on paper, and dried in a dark room to preserve the chlorophyll, which is useful as a coloring agent to delineate the patch site. After thorough drying, the plants are broken or finely ground in order to extract the maximum amount of oil. The

broken plant is loosely packed to within an inch of the top of a pint jar and covered with ether. The jar is sealed to prevent evaporation. The ether covered plant material should stand for a minimum of twenty-four hours. The ether containing the dissolved plant resin is filtered and is then placed in an open vessel to allow almost complete evaporation of the ether. To facilitate handling, evaporation of the extract is discontinued just before the liquid becomes too thick to pour. The residue is a very sticky, viscid substance, varying in color, according to plant species, from a very dark green to greenish-brown or black. Dilutions are obtained by dissolving the crude resin in acetone and are made by volume and not by weight. The 1:10 dilution is not a cutaneous irritant if properly applied.

Method of Strauss and Spain.— Freshly collected leaves are freed of twigs and injured leaves, placed in an oven at 40 to 50 degrees until the leaves are quite brittle. They are then rubbed through a coarse sieve and the leaf meal stored in dry sealed glass jars containing silica gel. The meal retains its activity indefinitely.

Ten grams of meal are added to 100 ml. pyridine. This stands for twenty-four hours in the refrigerator, and the meal is filtered off with a Buchner funnel. The filtrate is bottled as the stock solution.

To a 250 ml. sterile centrifuge cup are added 100 ml. sterile distilled water and 40 ml. pyridine-ivy stock solution. Mix and immediately add slowly while shaking 40 ml. sterile 0.25 N sulfuric acid solution containing 2 per cent potassium alum by weight. A fine green precipitate results. After mixing thoroughly, the centrifuge cup is capped with a sterile rubber stopper and allowed to stand for twenty-four hours in the refrigerator.

The tube is then centrifuged and the supernatant fluid removed by a 100 ml. volumetric pipette with a suction bulb attached.

Then 200 ml. sterile normal saline containing 0.4 per cent phenol are added. The precipitate is thoroughly mixed with the saline by a sterile rod, and it is then centrifuged and the supernatant wash solution is discarded. A total of four 200 ml. sterile saline washings are made. Then sterile normal saline containing 0.4 per cent phenol is added to bring the volume to 40 ml. Sterility tests are then run.

Care must be taken to mix the solution completely before making dilutions so as to obtain homogeneous sampling.

This extract may be injected without dilution further and is painless upon injection.

POLLEN AND PLANT DERMATITIS

We have given considerable space to the discussion of rhus dermatitis not only because of the extensive studies which it has received but also because it is the one variety of contact dermatitis in which desensitization has appeared to be effective. The same is true to a lesser degree with pollen dermatitis and other plant dermatitis. Specific therapy of other forms of contact dermatitis has so far been unsatisfactory.

Contact dermatitis recurring at the same time each year, especially in the warmer months, is usually due to plants.

Although the dermatitis under present discussion is customarily termed pollen dermatitis, it should be borne in mind that reaction may follow contact with other portions of the plant. In these cases dermatitis of the rhus type customarily occurs on exposed surfaces, especially the face and hands.

Symptoms occur only at certain seasons of the year, synchronous with the growth or pollination of certain plants. The following case history illustrates the usual sequence of events.

A professional man whose two favorite outdoor sports are golfing and hunting can golf through the spring and summer without misadventure. With the onset of the ragweed season each round of golf is followed by an episode of dermatitis of the face and hands. Patch testing shows him sensitized to ragweed pollen. With the advent of the hunting season he has similar experiences and, in addition, develops dermatitis about the ankles. He wears high shoes or boots and the presumption is that the pollen or other plant dust works its way down the trouser legs inside the boots to the ankles. In addition, when hunting he develops a patch of dermatitis along the right side of the chin. Patch tests show him sensitized to gun oil and to pyrethrum. Contact of the chin with the stock of the gun is responsible for the local flare-up. This man has taken treatment with pollen oil for several years, deriving enough benefit to justify continuance.

According to Brunsting and Anderson the first systematic reports of dermatitis caused by ragweed were those of Hannah (1918), and of Sutton (1919). Sulzberger and Wise reported positive patch reactions in 1930. In 1931 Brown, Milford and Coea reported that an oily substance in the plant was responsible for the contact dermatitis, and that this was different from the protein fraction responsible for hay fever and asthma.

Dermatitis due to pollens usually affects the eyelids, neck and exposed surfaces, especially above the collar line, the hands and ankles.

Testing.—In performing patch tests for ragweed dermatitis Brunsting and Anderson found that ripe, unwashed pollen gives as strongly positive a contact reaction as that caused by the leaf or stalk. The pollen is moistened slightly with olive oil. Scratch or intracutaneous tests with water soluble ragweed allergen in 13 cases showed positive reactions in but 2. In a few of the scratch tests, although there was no immediate urticarial or flare reaction, local dermatitis appeared after three or four days. They interpreted this as of the same significance as a positive patch test, due to the fact that after the scratch test the pollen and pollen oil had probably not been adequately removed from the skin.

Coea, in discussing the paper by Brunsting and Anderson, states that he uses the oil extracted from the leaf of the ragweed because it causes a much stronger skin reaction than that obtained from pollen which has been dried and stored for some time. He states that the oil in the leaf deteriorates rapidly under similar conditions.

Contact dermatitis due to pollen depends upon sensitization to the oil soluble fraction of the plant rather than the water soluble portion responsible for pollinosis. Brunsting and Bailey have successfully sensitized guinea pigs to pollen oil by local application. With daily application they found the incubation period to be from ten to thirteen days. The reaction was typically eczematous. The skin appeared to become generally sensitized since the reaction could be elicited at sites far removed from the primary reaction. Control tests with burweed marsh elder and other common test substances were negative, indicating specificity. Passive transfer was negative.

So far there have been but few reports of cutaneous sensitization of the contact type to the water soluble fraction of pollen. Chobot described a case of pollinosis successfully treated with the regular saline extract in 1934 who was tested endermally with ragweed extract in 1935. He developed a typical

immediate urticarial wheal but the following day returned with an extensive exuding dermatitis of the entire tested arm. This subsided after five days. Subsequent patch tests with the saline defatted extract and the purified albumin precipitate of the pollen produced typical local dermatitis. This patient appears to have experienced dermatitis from the pollen protein.

This is of interest in connection with studies that have been made on sensitization to water-soluble portions of plants. Vallery-Radot and his associates have studied grasses in an effort to determine what portions of the plant may cause allergic reaction in pollen allergies. Pollen extract and stamen extract gave equally strong reactions. The plant without these two elements still gave positive reactions, although less strongly so, while the root appears to have no antigenic properties.

Diagnosis and treatment. The general principles of diagnosis and treatment are similar to those outlined under rhus dermatitis. Coca has shown that the contact excitant may be extracted from the leaves of the pollinating plant and this is the customary procedure. This is undoubtedly the simplest procedure with those who are accustomed to make field surveys and can collect plants for extraction. Those who make their own pollen extracts from dried pollen grains may make contact extracts for testing as follows. When preparing extracts for use in pollinosis, first remove ether-soluble substances by thorough shaking in ether. Filter the ether suspension through paper, leaving the pollen granules as residue. From the latter, prepare aqueous extracts for atopic testing and therapy. Evaporate the ether from the filtrate to obtain the fat soluble residue. This may then be redissolved in acetone to form a concentrated solution from which serial dilutions are made in one of the appropriate oils as described above. Patch testing is to be done either with the residue or 1:10 dilution in oil. Treatment is to be commenced with that oil dilution which gives but a very mildly positive contact reaction. Commercially prepared pollen oil extracts are available.

Shelmire advocates the use of plant oils orally for the relief of plant dermatitis from any source. The method is described under rhus dermatitis. He found prophylactic treatment quite effective.

Reactions.—Reactions from treatment have been described. Vaughan and Pipes have reported a patient who was receiving ragweed oil treatment. He had had many injections without misadventure. Within two minutes after one injection he reacted with severe abdominal pain and excruciating headache. This lasted for five hours. There was very little associated urticaria and no asthma. There was no exaggeration in cutaneous symptoms. Following this reaction the patient was relieved of his ragweed dermatitis for several weeks. Black observed a violent urticaria coming on within a few minutes after a subcutaneous injection of *Parthenium* in oil. The reaction recurred on two subsequent occasions using the same dose. It was clearly not due to puncture of a vein. Previous injections had been well tolerated.

Shelmire finds anal pruritis and acute dermatitis from overdoses of the oral extracts.

Contact Allergy Due to Other Plants and Plant Derivatives

There can be no doubt that the allergic excitant responsible for contact dermatitis is much more active in certain plants than in others. This is especially true of the rhus and primula families. On the other hand, certain persons are undoubtedly more susceptible to contact sensitization than are

others. These two factors, (a) allergenic potency or virulence ("poisonous activity") and (b) allergic susceptibility, help to determine any number of specific contact sensitizations, some of which are high in frequency, some rare. There have been isolated instances on the one hand of sensitization to plant constituents or products that have been universally considered completely innocuous, and there are much more frequent instances of sensitization to products which through experience we have come to think of as potentially irritant. Examples of the former are the leaves, wood, sawdust and roots of



Fig. 273.—"Tulip fingers" type of dermatitis, usually occupational, associated with the handling of some vegetable, chemical, or other substance to which one is allergic.

otherwise innocuous plants. Examples of the latter usually include the sap or some product of the sap which contains the contact allergen in much higher concentration. In the former group two factors are usually active, individual predisposition and extensive or prolonged contact. Thus, *tulip fingers* or tulip bulb dermatitis usually occurs only in those whose occupation requires frequent contact with tulip bulbs and even then, only in those who are allergenically predisposed. Obviously, then, plant dermatitis often appears as an occupational dermatitis.

Allergy to plant saps and sap products.—One may say that all plant allergy is due to the presence of plant sap in some degree, but it is much more obviously so in some than in others.

Adhesive plaster dermatitis. While about one in six persons using adhesive plaster develops skin irritation therefrom, this is usually nonallergic, due to mechanical factors such as tension, friction, maceration due to heat and moisture, retained secretions, scratching, skin infection and breaking down of the capillaries. Only from one-half to one per cent have been found truly allergic to adhesive plaster. Grolnick has demonstrated that a large proportion of those with nonspecific adhesive dermatitis following the application of plasters under tension, also react to the same plaster applied without tension as a patch test.

U. S. P. adhesive is a mixture of rubber, resin and waxes with a filler of an absorbent powder such as zinc oxide, orris root or starch. Rubber is the coagulated latex or milk juice of certain tropical plants. Resin is the residue following distillation of the volatile oil from the oleoresin of species of the pine family. Olibanum, a gum oleoresin, also present in adhesive, is a plant juice derivative. Lanolin, purified wool fat free from water, and yellow beeswax obtained by melting and purifying the honeycomb are also constituents. Balata, a raw gum resembling gutta-percha, derived from the latex of the bullet tree is often present. Zinc oxide and starch serve as binders. Orris root is rarely used today.

Grolnick tested a series of 275 with these various constituents, finding that about one-sixth react nonspecifically. Only two of the entire series were shown to be specifically sensitized. In a five-year search he found an additional five not included in the study who were allergic to adhesive. He then tested these seven individuals with the various constituents finding all positive to resin and three to rubber. No positive reactions were observed to any of the other ingredients. Grolnick's incidence corresponds quite well with that of Bloch who found adhesive dermatitis in one among 200 normal Europeans and one among 100 eczematous patients.

Adhesive appears to be a rather poor sensitizer, as is also indicated by the fact that among some 200 workers engaged in manufacturing plasters, who manipulated the raw rubber and pitch by hand, Grolnick found no case of contact dermatitis.

Substitutes for patch testing.—The immediate interest in adhesive dermatitis lies in the fact that this material is used in patch testing. A positive adhesive reaction will often obscure the reaction to the test substance. To avoid this Grolnick and Walzer suggested the use of nonmoisture-proof cellophane and a special collodion as protective material.

Cellophane and collodion.—Grolnick states that when cellophane is used as the cover, it should be nonmoisture-proof, 600 weight. The proofing material contains a resin which has been found to cause contact reactions. The most practicable size for the cellophane discs is one and one-fourth inch diameter. A special nonirritating collodion is used.* It contains acetone-pyroxilin solution six parts, highly purified acetone two parts, highly purified amyl acetate two parts, sesame oil one-half part, ether two parts.

The collodion may be kept in a shallow, wide-mouth glass jar with screw cap, tightly stoppered. Thickening from evaporation may be corrected by the addition of acetone. The adhesive substance is applied with a test tube without lip, of diameter slightly less than that of the cellophane disc. The tube is dipped slightly into the collodion and a ring is transferred with slight rotation to the surface of the skin, following which, with the test substance already in place, the cellophane disc is fitted over the ring and held by gentle pressure with a gauze sponge until the collodion has dried.

The test substance if solid or in the form of a paste can be applied under the disc. If liquid it may be soaked into a small square of blotter or well-washed linen. These must not be supersaturated.

Several such tests may be applied to one arm and kept in place by a stockinette type of sleeve which is held in position at each end by a pair of adjustable elastic arm bands.

*This is prepared by Johnson and Johnson.

The discs are removed after twenty-four hours, the collodion being easily dissolved with acetone.

Duo adhesive.—Later Grolnick expressed preference for discs cut from white rubberized cloth, faced on one side only, applied with the rubberized side outside and sealed in the same manner with Duo Liquid adhesive. The latter is kept in jars and applied with a test tube in the same manner. Thickening in the jar is counteracted by the simple process of adding new duo from the tube.

When plant oils are used on the skin Shelmire advises against covering the patch with anything. Covered tests are prone to give much more severe reactions.

There are therefore available four procedures for patch testing: ordinary adhesive, Duo Liquid adhesive and rubberized cloth faced on one side only, the uncovered test, and plain cellophane with special collodion. One or more of these methods should enable one to circumvent confusing sensitization to patch test materials. With all methods there may be temporary nonspecific edema or erythema immediately after removing the patch which disappears in a few hours, after which the reactions appear more clear-cut.

Other plant irritants.—Schwartz, Abramowitz and Ewerts (1938) have reported contact dermatitis from *cocobolo wood*. Distribution in the latter case was to the face, scalp, neck, arms, hands and knees and attributed to carving a cocobolo cane. Patch tests were positive and cure followed avoidance. The active agent is said to be an ether-soluble resinous oil similar to the oily irritant in rhus.

Goldsmith (1943) reported dermatitis from *Semecarpus anacardium* (Bhilawanol or the marking nut). Sixteen postal workers developed a dermatitis from handling mail which had been contaminated with the oil from this tree. It is a member of the same family as the *Rhus* plants and grows in the hotter parts of India.

Perianal eczema involving the intergluteal cleft was found by Grolnick (1938) to be due to *Krameria* and oil of cade, constituents of "Dorb's Pile Ointment."

The writer has observed a woman with urticaria only at night, strongly allergic to *corn*. The excitant was traced to starched sheets. After *cornstarch* was no longer used on the sheets the urticaria cleared up.

A woman experiences dermatitis from contact with *morning glory vines*. She is not allergic to the rather closely related sweet potato. She is also subject to ivy poisoning.

Loveman described a woman with extensive stomatitis due to *anise oil* in a proprietary denture cream used for cleaning false teeth. There was dermatitis of the left palm, where she held the plate while cleaning it. Positive patch reactions were observed to the denture cream, oil of anise, anethol, the odor principle of the oil, and to oil of fennel (which also contains anethol). Avoidance cured the stomatitis and dermatitis. Intentional reexposure by eating anise gumdrops caused severe recurrence lasting over two weeks. Anise oil is used as a carminative and stomachic and as a constituent of some cough syrups. It is present in camphorated tincture of opium. It may be present in confectioneries. The seed is occasionally used in baking, and is one source of the flavor of certain liqueurs, especially anisette. It is found in certain gumdrops and in licorice. It is frequently used in perfumed soaps, toothpastes, denture creams, mouth rinses and perfumes. Anise oil is used on the skin in one per cent ointment for body lice and scabies.

Other causes of allergic stomatitis have included vulcanite dentures, hexyl-resorcinol toothpaste (probably due to an essential oil), *salvia* (*sage*) tea, the essential oil in *lemon peel*.

Loveman's case also reacted mildly to *oil of coriander* which he states may account for her having had mild stomatitis previously after eating dill pickles.

Pilot has observed dermatitis to *chrysanthemum* leaves in a florist, confirmed by patch test. Only the leaves caused symptoms.

Balyeat, Rinkel and Stemen report cases of contact dermatitis from *Helenium*. This plant occurs in every state of the union, abundantly in some. It grows along the roadside, in barnyards and wheatfields and is also used as a border in gardens.

Greenhouse and Sulzberger report sensitization to the *tansy* plant, proved by positive patch reaction and the reappearance of symptoms on reexposure. Symptoms were those of a contact dermatitis on the exposed surfaces, and hay fever when in the vicinity of the plant. They remark that the tansy is a common perennial rooted herb of waste places, kitchen gardens and waysides. It is a rank-smelling herb formerly popular as an abortifacient. It flowers from July to September.

Harville has reported contact dermatitis due to *Dicentra spectabilis*, commonly known as "*bleeding heart*." This is a plant frequently used in gardens. The case occurred in a greenhouse worker and was proved by positive patch test and reappearance of the dermatitis on reexposure. A patch test was made with pulverized leaves of bleeding heart. Pulverized leaves of primrose, chrysanthemum, begonia, geranium and aster were used as controls. Attempts at passive transfer were unsuccessful. Patch tests with ether extract and with alcohol extract were positive while extracts in alkaline extracting fluid were negative.

Although our great-grandmothers used *camomile* tea as a spring tonic, few of us today would recognize the weed. It is distributed through all the states except Florida, and rather abundantly in those bordering the Mississippi, the east central states, Virginia, North and South Carolina, and on the Pacific Coast. The variety of camomile (chamomile) known popularly as dog fennel contains a volatile oil and according to Rowe is a common skin irritant, responsible for some cases of dermatitis venenata. Rowe found that patch tests with other varieties of camomile than *anthemis copula* were less likely to be positive in sensitized cases. This is fortunate since the old spring tonic, *anthemis nobilis*, is a different variety and is occasionally used by brewers as a substitute for hops.

Dog fennel is widely distributed growing in vacant lots, barnyards, uncultivated ground and waste areas. It has a small yellow flower with petals somewhat resembling those of the daisy but with a pale or yellow center. The leaves are doubly pinnate, with linear pointed pinnae. The stems are slender, trailing, hairy and branched. Both leaves and flowers have a strong though not unpleasant smell.

Sternberg has described dermatitis of the scalp, neck and upper chest and back, proved by patch test to be due to an infusion of camomile leaves used as a hair dye. He also describes a dermatitis of the face due to oil of cloves in Ingram's Shaving Cream.

Levin reports the case of a sweeper in a department store with dermatitis of the hands proved by patch test and by recovery following avoidance, to be due to the handling of *sawdust*. The literature on sawdust dermatitis would indicate that satinwood, oak, teakwood, ebony, Japanese hardwood, rosewood, mahogany and birch have also caused dermatitis. The presumptive agents are various oils and alkaloids.

I have observed a man working in a paper factory who had extensive weeping dermatitis of both hands. Patch tests with several varieties of wood pulp and of *paper* were positive. Avoidance relieved him partially but not completely.



Fig. 274.—Contact dermatitis. Contact allergy to tobacco in an employee in a tobacco factory. Note involvement of areas in which contact is more likely to occur.

A young lady typist had dermatitis of the palmar surfaces of the tips of her fingers. She gave positive patch reactions to *carbon paper*. She was then tested with a number of brands and found that she was negative to and could use a high grade Dennison paper. This was probably due to the dye rather than the paper.

Lee studied a postman with dermatitis of the hands and legs due to contact with *newspapers* in the Post Office. Symptoms were always worse after

distributing the more voluminous Sunday papers. When in the course of his work he distributed newspapers into the letter box pigeon holes his nose would get stuffy.*

Lee describes the case of a woman with dermatitis of the vulva due to contact with *Kotex*. No tests were made but the condition cleared up after *Kotex* was no longer used. We have had a similar case, urticaria being relieved by discarding *Kotex*.

Huber describes dermatitis from *burweed marsh elder* in a man with symptoms only in the late summer and in whom positive patch tests were observed to the leaf of burweed. The leaves of ragweed and sunflower caused no patch dermatitis.

Smith has described dermatitis of exposed areas from sensitization to *creosote bush* (*Covillea glutinosa*), a plant which is abundant over a large part of the arid section of the southwestern states.

Caulfeild has described dermatitis of the fingers in handlers of *tulip bulbs*. The condition is known among horticulturalists as "tulip fingers." Since this was an occupational dermatitis, treatment with an extract in oil was given, with good results. Welker and Rappaport reported an additional case. This patient protected himself satisfactorily with rubber gloves while handling tulip bulbs. Passive transfer was negative.

Contact sensitizations have also been described to *daffodil*, *cinnamon*, *figs*, *prickly pear*, *hops*, *marigold*, *gaillardia*, *cow parsnip* and *orris root*.

I have observed positive patch tests in a single individual, to *pine needles*, *cedar*, *privet*, *abelia* and *clover*. He also reacted to silk and soap. About 20 control tests were negative. We have seen two additional cases of dermatitis due to *abelia* leaves, relieved by avoidance of contact.

Lancaster (1937) reports 12 cases of dermatitis venenata due to *clematis*. Kahn and Grothaus (1936) report contact dermatitis, angioneurotic edema and hay fever from *Parthenium hysterophorus* (bastard feverfew, false wormwood, Mexican bird seed), a weed distributed widely through the South.

Prosser White who has thoroughly reviewed the dermatologic literature lists the following additional plants as causing dermatitis of contact sites. Contact allergy has not been proved by patch testing as in the above cases but, by analogy, it seems to be the most probable explanation in most instances.

Rungus. This is a tree of the Malay Archipelago which is as carefully avoided by natives as is poison ivy in this country. It is stated that the tree is manipulated with impunity by some persons. A vesiculating dermatitis follows contact.

Vanilla. Vanilla dermatitis was recognized as early as 1883 and was described by Jonathan Hutchinson in 1892. It occurs in sorters, cleaners and packers and in factory workers, as a typical vesiculating dermatitis of exposed surfaces, and is attributed to the ethereal oil.

Silver Spruce wood has caused dermatitis in airplane factories.

Hop may cause what is known as hop-pickers' rash which is often accompanied by an acute catarrhal conjunctivitis known as hopper's eye.

Laurel has induced dermatosis of the hands and face.

Or eyed daisy, *milfoil*, *mayweed*, *Australian dogwood*, *geranium*, *eucalyptus*, *common ivy*, *daffodil*, *asparagus*, *oil of cassia*, *angelica* or *cow parsley*, *cow parsnip*, *wild parsnip*, *fig*, *tomato*, *tobacco*, *Virginia creeper*, *alderwood*, *satinwood*, *oak wood*, *chestnut wood*, *teak wood* are also listed.

*Lee, Howard, Oshkosh, Wisconsin. Personal communication.

Low has described a case which reacted to *bell heather* but not to ordinary heather; also a man who developed dermatitis when handling sheaves of oats or of barley but who did not react to contact with oatmeal or barley grain. He therefore selected weeds that were mixed with the sheaves and found positive reaction to *milfoil*.

Plants used in testing, by Shel mire, are listed in Table XIX, p. 222.

Foods. Food handlers occasionally experience dermatitis from contact with certain foods. Gelfand described a patient sensitized to *celery* root and leaves who also reacted to commercial oils from the leaves and seed. Hyposensitiza-



FIG. 275.—Combined atopic and contact dermatitis. Distribution on the body is characteristically that of atopic or neurodermatitis. The hands represent contact allergy to wool, in a seamstress. Scabies must, at times, be considered in differential diagnosis of atopic dermatitis.

tion was effective and the patient was able to continue at his occupation. He reviewed a few other cases from the literature occurring especially in workers in celery canning factories and mentions a similar dermatitis among parsnip gatherers in Belgium.

Zohn has described an unusual case of allergy to *spinach* in a vegetable dealer who developed dermatitis of the hands when handling spinach but in whom patch tests always remained negative. This patient also experienced gastrointestinal symptoms and asthma from the eating of spinach.

The writer has observed a food handler exquisitely allergic to a number of foods some of which caused dermatitis. These latter were radish, turnip, cabbage, cauliflower, broccoli, mustard, strawberry, peach, apricot, beans, grape, okra, parsley, celery, eggplant, pumpkin, squash, cantaloupe, cucumber, watermelon, lettuce, wheat, rye, barley, oat, corn, onion, garlic, rhubarb. Others, such as apple, pear, cherry, lemon, orange, grapefruit, banana, sweet potato, tomato, peppers, buckwheat, tea, coffee, cottonseed, honeydew, chicken, did not cause dermatitis.

Dermatitis from handling foods need not necessarily be due to the food itself. Traub, Gordon and Van Dyke (1937) report dermatitis of the face and arms from sensitization to yellow O-B (orthotoluene-azo-beta-naphthylamine) used to color oranges. They state that 90 per cent of Florida oranges in the New York market are artificially colored. Such oranges are stamped, "color added." The dye did not penetrate the rind, testing with the inside of the rind being negative.

Plant dust and house dust. Stroud (1935) found patients who complained of itching dermatitis while working around threshing machines allergic to an oil made from the dust brushed from the machine. He also found persons allergic to an oil extracted from house dust and reported relief by desensitization in both instances.

CONTACT ALLERGY TO ANIMAL PRODUCTS

Sensitization in this category is usually to furs, feathers or leather. The writer has seen contact dermatitis of the ear, usually more marked on one than the other, from contact with feather pillows. Avoidance with the use of dust-proof pillow covers provides relief.

Feathers.—Rostenberg and Sulzberger (1938) find goose feathers more highly reactive when used in the patch test than other types of feathers. They find feathers so frequently positive, especially in infantile eczema, that they recommend routine avoidance in this condition.

Furs.—Dermatitis of the hands in the winter time from fur-lined gloves (usually rabbit hair) is quite common. The writer has seen an artist allergic to the paintbrushes used in his professional work. Most high-grade brushes are of sable. So-called camel's-hair brushes are usually rabbit hair.

The fur of clothing has usually been through so many treatment processes that it is not highly allergenic, especially as an inhalant, but still may cause contact dermatitis which is usually easily suspected because of seasonal occurrence and location.

While the costly furs usually go under their true names, the less expensive ones rarely reach the ultimate consumer with a name which would enable one to recognize the original source. Often the name implies an entirely different animal. A muskrat hat, for example, was made of cat hair. The following is a list of the more important furs that are usually altered and sold under different names, as listed by Feinberg.

SPECIES	ALTERED AND SOLD AS:
Hare, dyed	Sable or fox
Hare, white	Fox
Rabbit, white	Ermine
Rabbit, white, dyed	Chinchilla
Rabbit, dyed	Sable
Rabbit, sheared and dyed	Seal, electric seal, Hudson Bay seal, muskrat

Muskrat, dyed	Mink, sable
Muskrat, pulled and dyed	Seal, Hudson Bay seal, electric seal, Red River seal
Mink, dyed	Sable
Marmot (woodchuck)	Mink, sable, skunk
Opossum	Beaver
Goat	Bear, leopard
Fitch, dyed	Sable
Kid, dyed	Lamb
Otter	Sable
Nutria	Seal, beaver, otter

Fur dermatitis is especially likely to occur among trappers and furriers. Much dermatitis apparently due to contact with furs is actually due to the fur dyes.

Clothing.—Contact allergy to clothing often involves animal substances. Winter dermatitis of the wrist may be due to the sleeve of a chinchilla overcoat. Dermatitis of the neck may be due to a silk scarf, fleece collar, etc. Contact dermatitis has been described as due to mohair (goat hair) upholstery



Fig. 276.—Contact dermatitis to animal hair. Involvement of the wrist and thumb from contact with a camel's-hair overcoat.

and clothing. I have seen dermatitis of one cheek in a person with positive patch reaction to wool, which was relieved by the simple expedient of having the patient protect the face from contact with a wool blanket at night.

Felt as an article of clothing usually applies to hats. The majority of felt hats are made of some kind of fur although the cheaper ones are of wool. The next higher grade contains hare and rabbit hair. The most expensive hats are made chiefly of beaver while the intermediates are of nutria. The writer has never traced inhalant allergy to felt hats.

Leather.—Here sensitization may be to the leather itself or to a dye. Paraphenylenediamine or ursal, a black dye which is very widely used on leather, fabrics and even occasionally as a hair dye, is a frequent offender. This compound after oxidation enters readily into firm chemical union with protein. This fact probably explains the ease with which many become sensitized to it, and explains its value as a fur dye. Hatband dermatitis and watch strap dermatitis on the wrist are not uncommon. Occasionally dermatitis of the foot or ankle may be traced to leather sensitization. Sulzberger and Kerr have described dermatitis of the wrists from boxing gloves.

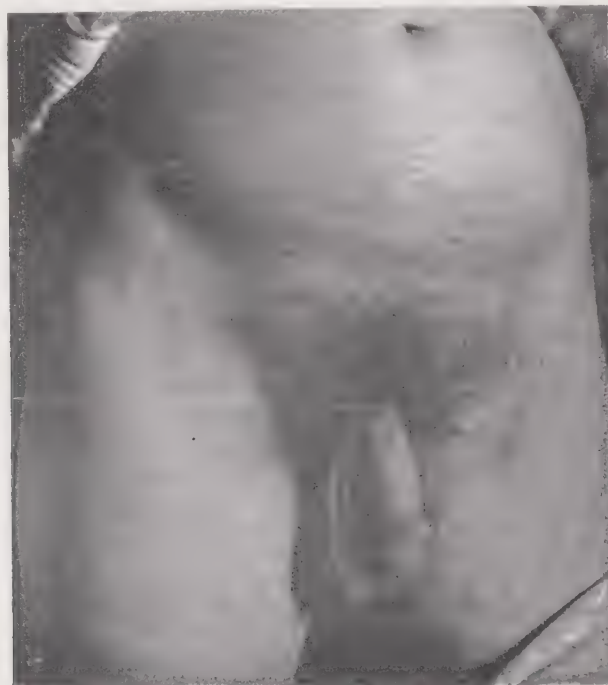


Fig. 277.—Leather dermatitis from contact exposure to a truss.

Schwartz (1936) reports wrist watch strap dermatitis due to "Oil Yellow T" (amido azotoluene). This, used with amyl black, produces a fast black color. The latter dye was found nonallergenic in the cases studied.

The following cases from the writers' experience are of interest. The first had dermatitis of the hands traced to leather, which cleared up on avoidance until the following spring, when he again took up golf. Recurrence from handling the leather grips on the clubs was relieved by taping them with adhesive. The second found that a dermatitis of the left palm was due to a leather cover on the steering wheel of his car. Its removal resulted in cure, followed some months later by a new patch of dermatitis on the thumb and first finger of the right hand. It required some time before he realized that the later eruption was due to inadvertent handling of his key holder in his right trousers pocket. We have also seen contact dermatitis of the groin from a leather truss.

Hexa-nitrodiphenylamine, commercially called aurantia, has been used for years to stain cheap leather goods. According to Low, during the war many cases of dermatitis occurred from wearing helmets and hats lined with a leather substitute stained with aurantia. This same dye was in explosive

bombs during the World War. When the bombs exploded they scattered a fine yellow powder which clung to the skin and caused no dermatitis until about nine days later (presumably the period required for sensitization).

Other causes.—Contact dermatitis of the hands due to fish glue, seen in a library worker, might be classed as of animal origin.

A friend of the writer regularly develops urticaria of the hands when his hound dogs lick them. Contact with dog hair causes no trouble. Skin reaction to dog hair is negative. When other breeds of dogs lick his hands, he does not get urticaria.

CHAPTER LXVIII

CONTACT ALLERGY TO DRUGS, CHEMICALS AND COSMETICS

Contact Dermatitis Due to Drugs

Low has described contact dermatitis with vesiculation among employees engaged in the manufacture of *morphine* and *strychnine*. *Iodoform* which was used much more widely twenty-five years ago often caused contact dermatitis. Dermatitis of the hands from *novocain* and *procain* is rather frequent especially among dentists. Other drugs include *formalin*, *oil of citronella*, *scharlach R.*, *phenylhydrazine*, *lysol*, *cresol*, *atropin*, *lanolin*, *quinine*, *resorcin*, *tar*, *ephedrine*, *hexylresorcinol*, *the arsphenamines*, *tincture of benzoin*, *nupercain*, *calmitol*, *chloral*, *mercurochrome*, *iodine*, *bichromates*, *balsam of Peru*, *mustard*, *flaxseed* and *belladonna* plasters, *butesin picrate*, *picric acid*, *mercury*, *sulfur*, *arsenic*, *bichloride of mercury*, *medicated alcohol*, *turpentine*, *metaphen*, *potassium iodide*, *sudan III*. The list is obviously not complete. Given sufficiently prolonged exposure in one predisposed to cutaneous sensitization it would appear that almost any drug or other substance may eventually be added to the list.

Some of the medications mentioned could logically be classed in the preceding chapter, as plant derivatives.

Ephedrine not infrequently causes contact dermatitis, usually around the nose and upper lip, after prolonged local use in the nose. The nasal mucosa may also be reactive, in which case the symptoms are of vasomotor rhinitis. Hollander (1936) has reported dermatitis of the penis in a pollinosis case occurring when the patient neglected to wash his hands after using an ephedrine nasal spray prior to urination. It is of interest that patch test on the arm with ephedrine was negative but direct application of a spray to the penis caused an intense contact dermatitis. This is illustrative of the occasional case in which positive patch tests can be obtained only by application of the substance on the area usually involved in dermatitis.

Nelson reported eczema of the hands which spread rapidly following local application of 2 per cent *oil of cade* ointment. Patch tests showed strong reaction. Alden and Jones have reported dermatitis venenata of the eyelids following the use of *physostigmine salicylate* in the eye. The writer has observed two persons allergic to "Vick's" preparations. One developed contact dermatitis of the neck from salve, the other vasomotor rhinitis from nose drops.

Abramowitz and Noun remark that when *chloral hydrate* was used extensively there were few reports of idiosyncrasy. Most of the few discussions dealt with idiosyncrasy to chloral when taken by mouth, although there have been some reports of dermatitis from contact with ointment containing chloral. They report the case of a druggist with dermatitis of the hands resulting from occupational contact with the drug. Repeatedly the hands cleared up on avoidance and broke out again after contact. Patch tests were positive down to 1 per cent concentration and were negative on controls.

Ford reports a case of contact dermatitis due to *quinine*, confirmed by a positive patch test to the drug, and manifested by a vesicular dermatitis of the face, scalp and neck following two applications of Kreml hair tonic.

Several months later the same patient returned with a similar dermatitis involving the penis, scrotum, eyes, cheeks, ears and sides of the neck. It first started on the genitalia. This time the etiologic agent was found to be a contraceptive vaginal suppository containing quinine bisulphate and boric acid in a cocoa butter base.

Vaughan and Fowlkes have described dermatitis of the penis in a man allergic to cocoa whose wife used a contraceptive suppository with a base of oil of *theobroma*.

Sulzberger and Kerr report an inflamed vesicular dermatitis of the scalp, face, eyelids and neck from allergy to a hair tonic containing quinine, widely advertised as a dandruff cure.



FIG. 278.—Patch tests. The substances tested may be recorded on the adhesive covering.

Sulzberger and Kerr report an interesting case of *calmitol* sensitization, a man with dermatitis of the left hand and wrist, the sides of the neck and the genitalia. He himself did not use calmitol, but his wife had been using it for chronic pruritus vulvae. Upon her discontinuing it, the husband's dermatitis disappeared.

Sulzberger and Kerr report *Mazon ointment* dermatitis in a woman who did not use the ointment herself but whose daughter did. She developed symptoms after repeatedly washing her daughters' clothing.

Sulzberger and Morse have reported contact dermatitis from *wool fat* (lanolin). This is often used as a base for ointments. As has been said in the discussion of trichophytosis it happens not infrequently in dermatologic practice that a patient becomes sensitized to the *therapeutic ointment*. If therefore a patient who is being treated locally with an ointment or other local medication inexplicably gets worse, the possibility of sensitization should be considered and patch tests should be done with the ointment. Patients with

dermatitis of long standing who have tried many ointments should be tested with the various ones. Occasionally all that is necessary for cure is total discontinuance of local applications. It is well before prescribing any new ointment to do patch tests with it.

Gelfand has described dermatitis of the scalp and neighboring portions of the skin from "liquid arvon," a proprietary hair tonic containing salicylic acid, resorcin and *potassium arsenate*. He found the third constituent responsible for symptoms. One should test with each of the constituents. Ayres and Anderson have described sensitization to salicylic acid. We have seen sensitization to resorcin in hair tonic.

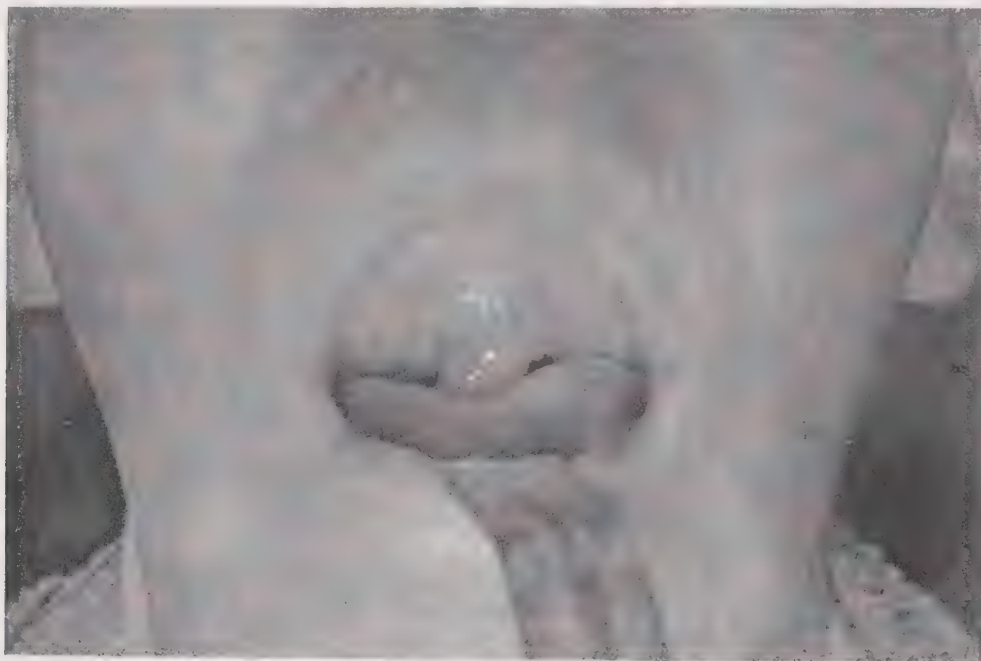


Fig. 279.—Contact edema of the uvula due to neosynephrine repeatedly instilled into the nose over a long period for relief of allergic coryza.

Chemical Dermatitis

Here again the list is so long (and increasing rather rapidly) that it hardly seems worth while to attempt to enumerate all of the chemicals which have been shown responsible for dermatitis. Certain of the dyes used in dyeing clothing, leather goods, and other materials and dyes in cosmetics are frequent causes of trouble. Some chemicals which are normally not at all irritating may become allergenic, while others which are mild irritants may become extreme irritants to some persons. Some contact agents to which most of us are rarely exposed may be commonplace to a person working with them. Consequently much of the contact dermatitis that we are called upon to treat falls properly in the category of occupational dermatitis. It should be borne in mind that not all occupational dermatitis is allergic. Natural irritants, infections, and sometimes just plain dirt and trauma contribute their part.

Dyes.—Dye dermatitis is often occupational. McCafferty states that from 1 to 2 per cent of individuals are susceptible to the toxic effect of anilin. Ingram states that 4 per cent of normal individuals show a "natural" idiosyncrasy toward paraphenylenediamine.

Criep has recently reported dermatitis from Easter egg dyes.

Occupations and possible contact excitants are listed in Tables LXVIII and LXIX.

TABLE LXVIII.—OCCUPATIONAL EXCITANTS*

OCCUPATION	AGENT PRODUCING DERMATITIS
Autotypers	Bichromate.
Bakers	Flour or sugar, possibly related to the arsenic content, also to cottonseed oil and potash; the former being used in bread, the latter in pretzels.
Barbers	Quinine, resorcin, mercury, and sulfur in hair tonics.
Bronzers	Arsenic.
Burnishers	Mercury.
Chemists	Many irritants handled by them.
Compositors	Benzine or bichromate.
Cooks	Patent cleaners, strong soap, kitchen insecticides.
Dentists	Novocain.
Electroplaters	Cyanide and various acids.
Electrotypers	Copper sulfate and hydrochloric acid.
Exterminators	Action of arsenic, formalin, sodium chloride or pyrethrum.
Foresters	Poisonous shrubs and sprays.
Furriers	Arsenic and paraphenylenediamine.
Gardeners	Plants, arsenic, insecticides, lime dust, and fertilizers.
Grocers	Handling of sugar and flour.
Interior decorators	Artificial coloring in fabrics.
Jewelers	Cyanide.
Milliners	Dyes and arsenic.
Munition workers	Various explosives.
Nurses	Bichloride, formalin, medicated alcohol, lye or other antiseptics used in scrubbing up.
Painters	Turpentine, varnish remover, arsenic, linseed oil, and aniline dyes.
Photographers	Pyrogallol, metol or caustic soda.
Photogravure workers	Paranitralin red.
Photostatic operators	Chromates.
Piano workers	Aniline dyes and arsenic in felt.
Polishers of metal	Oxalic acid, turpentine and bichromate.
Printers	Arsenic, artificial coloring and hydrocarbons in inks.
Soap workers	Strong alkalis.
Surgeons	Antiseptics used in scrubbing up.
Tanners	Bichromate and hydrochloric acid.
Washerwomen	Patent cleaners, strong soaps and roach powders.

*Andrews: Diseases of the Skin. W. B. Saunders Co., Philadelphia.

Dyes taken internally.—Skin eruption due to aniline dye products need not necessarily be due to contact exposure. Baer described a woman with an erythematous maculopapular eruption of the neck, shoulders, arms and forearms, on covered and uncovered areas who also had nausea and cramps coming on from 2 to 3 hours after meals, sometimes with associated diarrhea. There was no history of allergy. The condition responded to palliative dermatologic therapy but recurred after several months. Food tests were found negative and a green coloring matter used in gelatin came under suspicion. This was described as containing 2.6 per cent certifiable aniline color. When she ate the green gelatin on trial, dermatitis returned. When the same brand of gelatin without the green color was eaten dermatitis did not appear. Patch and passive transfer tests were negative.

Fifteen coal tar dyes have been approved by the Food and Drug Administration for use in foodstuffs.

Baer states, "The response of the patient to the aniline dye was a general one, not based on an idiosyncrasy; hence it was a toxic rather than an

allergic reaction. The procedures that are used to demonstrate allergy (passive transfer, scratch, patch and intradermal tests) were entirely unproductive." Later, he remarks, "This reaction may be regarded as similar to the gradual development of a sensitivity to drugs such as arsphenamines, amidopyrine and quinine. I believe that over a protracted period this patient has become sensitized to the aniline dye in a manner similar to the development of idiosyncrasy after exposure to the hair and fur dyes."

TABLE LXIX.—SPECIFIC EXCITANTS OF CONTACT DERMATITIS, OCCUPATIONAL GROUP*

GROUP	INDIVIDUAL MEMBERS
Dye intermediates-----	Aniline compounds, nitro compounds, nitroso compounds, dinitrochlorbenzol, naphthalene and compounds, anthracene and compounds, benzidine and compounds, benzanthrone compounds.
Fur dyes-----	Paraphenylenediamine, para-amido-phenol, aniline black.
Leather dyes-----	Nigrosine, Bismarck brown, amido-azo-toluene hydrochloride.
Photo developers-----	Paraphenylenediamine, paramido-phenol and compounds, hydroquinone, metol (sulfate of monomethyl paramidophenol), pyrogallol.
Soaps-----	Those containing free alkali, olive oil "foots" or coconut oils, medicated or perfumed ones.
Rubber compounds and impurities---	Wild rubber, hexamethylenetetramine, guanidines, tetramethyl-thiuram disulfide, phenyl beta-naphthylamine, para- and orthotoluidine, tri-ethyl, trimethyl triamine.
Insecticides and fungicides-----	Mercury, arsenic, fluorine, nicotine, pyrethrum or compounds.
Explosives-----	Tri-nitro-toluene, tetra-nitro-methylaniline, fulminate of mercury, tri-nitro-resorcin, sensol, lead styphnate.
Cosmetics-----	Containing irritant dyes, oils and perfumes and other chemicals.
Oils, vegetable and mineral-----	Essential oils, sulfonated oils, cutting oils, coning oils, petroleum distillates.
Fabric dyes-----	Crystal violet, malachite green; auramine, chrysoidine R, metanil yellow, chrome mordanted dyes, amino-azo-benzol, brilliant indigo 4G, black X dye, erio black, hydron blue, inanthrene violet R. R., ionamine A. S., methyl violet, pyrogene violet brown, orange Y, orange R, safranine, sulphanthrene pink F. F., Victoria blue, Victoria green.
Rosin, synthetic resins and waxes---	Rosin, wood rosin, burgandy pitch, dammar, phenol formaldehyde resins, urea formaldehyde resins, trichloronaphthalene (halowax), all chloronaphthalenes, chlorinated waxes.

*Schwartz: U. S. Public Health Reports.

As long as people continue to believe that positive skin test or passive transfer is necessary for the demonstration of allergy, apparently paradoxical statements such as this will continue to appear. The author does not take into account the large number who have steadily ingested the same dye product without symptoms. He further states, "Interest is aroused not only by the natural sensitivity of the patient to such a dye but by the ease with which the sensitivity can be acquired." The point of view would have been changed if he had added one phrase to the last sentence, "the ease with which the sensitivity can be acquired by an *occasional* individual."

Clothing. Dermatitis from clothing is not necessarily due to the original cloth material. It may be due to the dye or to chemicals employed in "finishing" the goods. This is brought out in the work of Schwartz in his investigation of stocking dermatitis.

A "finish" is used to soften fibers or to give fabric a "crunchy" texture, to give a fluffy texture to wool, to render fabric relatively waterproof, or to diminish lustre. The finishes used in men's socks are usually sulfonated oils or fats, especially sulfonated castor oil or olive oil used alone or mixed with mineral oil, unsulfonated oils or borax. Women's hosiery may be rendered somewhat waterproof by treating with starches, gums, gelatins, Japan wax, beeswax, paraffin or other waxes. Inorganic salts used to diminish lustre include zinc sulfate, barium sulfate, aluminum sulfate and titanium oxide.

Schwartz (1941) discussed the use of synthetic resins in fabric finishes as a cause of dermatitis which needs attention.

Dresses.—Goodman and Sulzberger describe a characteristic picture for dress dermatitis. Most of the women were middle-aged and overweight, subject to hyperidrosis, particularly of the axillae. Dermatitis affects the axillae and periaxillary regions but spares the pit. This is of diagnostic importance since the pit is usually involved in moniliasis, seborrheic dermatitis and



Fig. 280.—Nickel dermatitis of the neck due to a so-called "platinum" pendant.

psoriasis. With more extensive involvement the antecubital spaces, the sides of the neck where the dress touches and extending down to where the underclothes protect, may be involved. In severe cases the extensor surfaces of the arms, thighs and buttocks and the entire face may be involved. They saw no cases with involvement of the hands or below the knees. Even in the generalized cases, the axillae and antecubital spaces were most severely involved. The dermatitis is of the character of contact eczema. Some cases have associated axillary sweat gland abscesses and furuncles. The authors believed that allergy to dress materials may even play a part in the causation of hidradenitis, appearing without manifest dress dermatitis. There is often an associated seborrhea of the scalp. Patch tests with the particular dress materials under suspicion were usually positive. It is not sufficient to test with any black dress material. It must be the particular black dress material under suspicion.

Since some patients show polyvalent sensitivity, reacting to different shades and colors, it is difficult to advise the patient beforehand which shade or color will prove harmless. In some instances of marked polyvalent reactivity, it was necessary to test the patient with material from each new dress before it was purchased.



Fig. 281.—Dress dermatitis. Note distribution below neckline of dress, and above the top line of the slip.

Men's clothes. The distribution of clothing dermatitis in man is different. Here the legs are involved from the ankles to the lower edge of the underwear. Popliteal spaces and posterior and inner aspects of the thighs are involved; extensor surfaces less so. The lower border may stop at the shoe

top or extend on to the feet or toes. The eruption is not as acute as it may be on females, usually not vesiculating. It is chronic, erythematous, scaly and somewhat lichenified and infiltrated. Pruritus is severe. The neck and wrist may be involved. Polyvalent dye reactivity may be present.

The condition may be occupational, occurring, for example, in tailors and sewing machine operators. Treatment recommended by Goodman and Sulzberger includes avoidance, soothing lotions, x-ray treatment. Even so, several months may elapse from the time of last exposure to complete freedom from symptoms.

Substances on clothing.—Baker (1938) has reported contact eczema from wearing dresses which had been hung in a closet with paradichlorobenzene. Cakes of this chemical volatilize and are used as a moth preventive. Patch test was positive and cure followed removal of the cake and cleaning of the dresses.

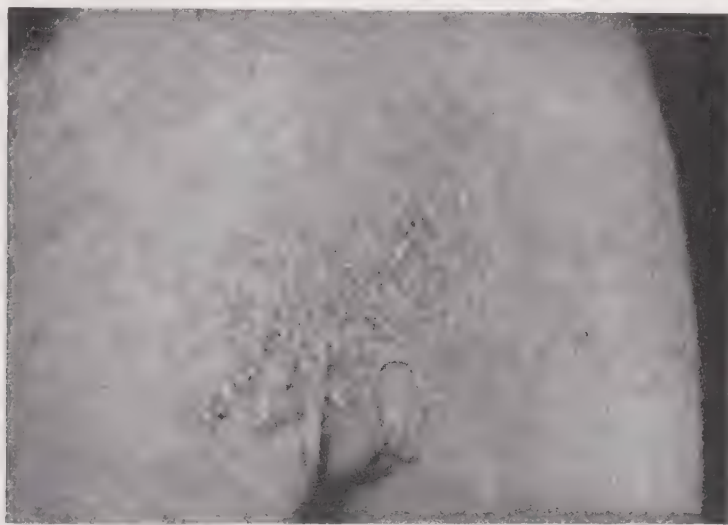


Fig. 282.—Dress shield dermatitis of the axilla.

Method of preventing dress shield dermatitis.—Schwartz and Andrews (1938) find that the irritation occurring in some people from contact with thin rubber goods may be due to the chemical used in processing. Thus thin goods such as the rubber in dress shields, condoms, surgeons' gloves, are usually vapor-cured with sulfur monochloride. Hydrochloric acid is a byproduct which is often not completely neutralized in the processing and becomes a potential irritant. Heat, moisture and friction predispose to irritation by the acid. Perspiration appears to soak the acid irritant out of the rubber and into contact with the skin. Such cured rubber goods which are to be worn next to the skin should be neutralized with ammonia vapor. The wearer who finds these materials irritating should soak the rubber in a mild alkaline solution of soap and sodium carbonate and rinse well. After this the materials are usually no longer irritating.

In this type of dermatitis Schwartz and Andrews observed negative patch reactions. We are dealing more with chemical irritation than with allergy. Their investigations were with dress shields and sanitary belts.

Stockings and socks.—Schwartz reports linear dermatitis due to a dye used in coloring stripes in rayon hose. Another patient was unable to wear

new unwashed black rayon socks without consequent dermatitis, although the same socks after being carefully washed caused no reaction. Here the symptoms were found due to certain finishes, sulforicinol S, sulfonated castor oil, borax, and olive oil soap. The finishes are usually washed out in laundering.

Black dyes commonly used in the coloring of hose are "direct black," "Zambesi black," "sulfur black," and "aniline black." Persons with a tendency to dermatitis after wearing new socks or stockings would do well always to have them washed before first wearing.

The fact that dermatitis from clothing may be due not only to the cloth itself but also to the dyes and finishes explains the failure of allergists at times to recognize the offending material. If silk is suspected it is not sufficient just to patch test with silk or with simple uncolored silk cloth. The actual material being worn often must be used. This comes to the point where, when black stockings are suspected, it is not enough to test with any black stockings, but the trial must be made with the particular black stockings under suspicion.



Fig. 283.—Shoe leather dermatitis. Note lack of involvement of the interdigital area. Leather inside the shoe as well as outside may cause symptoms.

Goodman and Sulzberger (1938) report an extensive study of sensitization to dyes in clothing and lipsticks.

Their investigation of sensitization to dress materials revealed positive patch reactions to materials of many colors (not to blue alone as reported previously by Bonnerie and Genner). Patch tests with a large group of dyes on men with dermatitis for which the causal role of clothing (suits) was suspected indicated that in these cases also dyes may be excitants.

Shoes.—In a series of cases of shoe dermatitis they found that the leather dyes are chiefly responsible. Some are allergic to black dyes, others to brown. In one case there was such marked reaction to a constituent (probably a dye) in a shoe polish that a single wearing of a shoe to which this polish had been previously applied would cause an exacerbation of a dermatitis of the feet.

Differential diagnosis.—Differentiation from dermatophytosis is important. All cases in the series studied by Goodman and Sulzberger had previously been diagnosed and treated unsuccessfully as ringworm. They list the

following distinguishing characteristics: (1) There is usually little or no involvement of the interdigital spaces. (2) Contact areas between the toes are usually not involved. (3) There is a characteristic involvement of the tops of the toes, particularly the great toes. (4) Maximal eruption is likely to be at the sites of maximum pressure or friction such as the dorsal aspect of the foot, the instep, the lateral and medial aspects of the heel, the periphery of the sole and the dorsal and lateral aspects of the little toes. (5) There is a tendency for the eruption to be demarcated by the shoe margins. (6) Treatment as a dermatophytosis has usually been unsatisfactory. (7) Itching is usually more severe than in uncomplicated dermatophytosis.

The eruption is usually of the contact type with various degrees of erythema, scaling and vesiculation. Some react to brown leather, others to black. Those reacting to brown may not be able to wear black shoes because of the brown leather on the inside.

Fungus infection may coexist and may possibly predispose to dye sensitization.

When sensitization is to shoe polish, the lesion is likely to be on the ankles just above the shoe margins.

Duration of reaction.—Especially interesting was the observation that, in highly reactive persons, a simple contact exposure might produce an exacerbation that persists several weeks in spite of the absence of further contact.

Rubber and composition material.—J. M. Feder has told the writer of a woman allergic to rubber who developed angioneurotic edema of the lips and gums after a basal metabolism test. The attending physician wished a sample of stomach contents. After the injection of 5 drops of adrenalin, the duodenal tube was passed without untoward symptoms.

An artist in the writer's experience was allergic to the rubber cement used in mounting pictures and to the rubber of art erasers. Symptoms were of contact dermatitis. Vaughan and Fowlkes have described local dermatitis due to rubber condoms.

A man had a ring of dermatitis of about two inches' diameter involving the chin and upper lip. This was traced to contact with the composition mouthpiece of a dictaphone. Several years previously he had had the same type of eruption when wearing horn spectacles, which was relieved when he changed to metal earpieces.

Cosmetics

Five thousand years before Christ, Queen Shub-ad of Ur painted her nails and plucked her eyebrows; 3500 B.C. in Egypt cosmetics were classified as: unguents; perfumes; creams; pomades; rouges; powders; eye stain and nail stain. But long before either of these, the earliest savages, male and female, adorned their bodies for the sake of beauty, with paints and dyes as they do today.

The word cosmetic is derived from the Greek *Kosmos*, meaning "I adorn."

Goodman and Sulzberger found that the great majority of contact cheilitis was caused by some ingredient in lipsticks, most frequently tetrabromfluorescein dyes and azo dyes. Analysis of patch test reactions usually permitted the preparation of a lipstick which was free of the culpable dye and which the pa-

tient could use with impunity. They observed one unusual case in whom a general urticaria was relieved after a lipstick responsible for cheilitis was discarded.

Downing has contributed an interesting review of the use of cosmetics, past and present. They were well known to the ancient Egyptians who painted the eyes with a green ore of copper (malachite) or a grey ore of lead (galena); colored their cheeks with red oxide of iron (ocher); the hands, nails, feet and hair with henna; and who, for perfume, used frankincense and myrrh.

As skin beautifiers, skin tighteners and wrinkle removers the ancient Romans used honey, barley, egg washes, seaweed and other slimy substances and asses' milk. Eyebrows were painted, and rouge from vegetable dyes was used. Chalk and white lead were applied to whiten the face. The Romans dyed and bleached the hair. We may conclude, then, that cosmetics are by no means new. They have, to be sure, become more general. In Roman days the principal users according to Downing were the courtesans and the sport classes.

The following brief statements are extracted from the very excellent monograph of Schwartz and Peck (1946), which should be consulted for more detailed information.

Face powders may contain talc, kaolin, calcium and magnesium carbonates, starch, titanium dioxide, zinc oxide, lithopone, barium sulfate, lycopodium, zinc and magnesium stearates, and powdered silica. A heavy powder may contain a large amount of zinc oxide or titanium dioxide; a light powder contains less of these. Colors are usually aluminum, calcium, barium, or other metal lakes of aniline dyes or oxides of iron, ochres, umbers, etc., or mixtures of these.

Perfumes may contain natural flower oil or blends of many odorous chemicals. They contain a fixative agent which may be of animal origin such as musk, civet, ambergris, skatole, castor, and indole, or they may be an aromatic resin. Bergamot may be used, and it should be remembered that it is a photosensitizing agent.

Bleaching and freckle creams most frequently contain ammoniated mercury, mercuric chloride, lactic acid, acetic acid, potassium hydroxide, salicylic acid, and resorcinol. Sometimes the perborates, hydrogen peroxide or zinc peroxide, may be used.

Astringent creams may contain zinc sulfate, aluminum sulfate, or bismuth subnitrate. They may also contain resorcinol and salicylic acid.

Cleansing cream usually contains mineral oil, beeswax, borax, possibly lanolin, and water.

Vanishing creams are made up of stearic acid in the stearates of sodium, potassium, ammonium, or aliphatic amino derivatives. They may contain glycerine, propylene glycol, cocoa butter, mineral oil, lanolin, and such synthetic esters as glyceryl monostearate.

Lipstick base may contain beeswax, castor oil, cocoa butter, lanolin, and mineral to which are added various fluorescent dyes.

Nail lacquer usually consists of cellulose nitrate, acetone, triethyl phosphate, resin, alcohol and dye.

Many other materials are used and, as fashions change, the materials and the composition of them may change. The above will serve to give only some idea of the complexity of the matter. The manufacturers of "hypoallergic" cosmetics will supply the formulas which they use and materials with which to test patients who are suspected of being sensitive to their products. The composition of other cosmetics usually has to be conjectured.

Blepharitis.—Rattner has reported five cases of dermatitis of the eyelids due to various causes. The first, a severe acute dermatitis involving the lids and adjoining parts of the face, was due to "Godfrey's dye." The eruption was so acute that two months elapsed before the patient could return to work. The cause in the second case was found to be a wave-set preparation. The third was caused by a face lotion containing camphor. The fourth was due to cold cream. This patient had used the same cold cream for years before symptoms became manifest. Patch testing was positive and caused a focal flare-up. The probability is that some new ingredient, such as a new perfume, had recently been added to the cold cream formula. The fifth case was due to contact with imitation horn spectacles.



Fig. 284.—Cosmetic dermatitis of eyelids.

The most frequent causes of dermatitis of this portion of the face are creams, eye washes, nasal sprays, face powders, nail lacquer and, less frequently, spectacle rims.

Fatal conjunctival reaction.—Forbes and Blake have reported a death following the application of "Lash-Lure." Within thirty seconds after plucking the eyebrows and the application of Lash-Lure the tissues commenced to "burn and swell." Pain was so severe that the second eye was not treated. Intense conjunctivitis ensued, followed by *Staphylococcus aureus* infection. Infection spread to the tissues of the eye and the patient died on the eighth day. The writers point out that plucking of the eyebrow before application of the dye would furnish multiple portals of entry of the dye equivalent to multiple skin tests applied to a small area. Death appeared due to a violent local and systemic allergic response, with superimposed infection.

Other cases of dermatitis from eyelash preparations have been reported.

Sulzberger and Kerr report three additional cases of allergy to cosmetics, two with dermatitis, due to a new face powder—Chanel's Une Idée. The third was allergic to Paquin hand cream.

Nail lacquer is a frequent cause of dermatitis about the face and neck, seldom about the hands. It is probably the most frequent cause of dermatitis about the eyelids. One patient was seen with a collar of eczema about her neck

due to coating a metal necklace with colorless nail lacquer. With the advent of the "up sweep" hair style and the use of lacquer to hold the hair in place, many cases of dermatitis of the ears, side of the face, and neck have been seen. Most of these were due to certain brands which were removed from the market.

Author's Notes on Cosmetics

The safest eyebrow pencil is mascara (lamp black) in wax or paraffin.

The majority of dry rouge powders contain no orris root or rice starch. They often contain gum acacia as a binder. The majority are colored with coal-tar dyes. Although there are special so-called nonallergic talcums and face powders, which do not contain orris root, the majority of proprietary cosmetic manufacturers today do not use this substance. The chief difficulty today is that since their formulas are secret, one cannot know what other possible allergens are being used.



Fig. 285.—Soap dermatitis. As is so often the case in contact allergy and other forms, multiple etiologic factors play a part. This patient's primary condition is contact dermatitis due to soap and various artists' materials. He is also allergic to a number of foods, whose ingestion results in exacerbation in his "contact" dermatitis. The condition was greatly relieved by changing from soap and the old-fashioned razor to the more modern dry electric shaver. Note limitation of lesion at the collar line. Also barrel chest due to associated asthma.

Every person using hair dye, whether it be an anilin dye (paraphenylenediamine, para-toluylene-diamine), a metallic dye (lead, copper, silver, iron) or a vegetable dye (henna, indigo, walnut) should be patch tested prior to treatment, and especially so after the dye has already been used one or more times (possibility of previous sensitization).

Nail polish was originally simple collodion solution. The newer polishes are nitrocellulose lacquers. Lacquer removers are varnish removers, especially acetone, or ethyl acetate. Sometimes oils are added. Cuticle removers are as a rule basically caustic potash with glycerin, water and perfume.

Hand lotions usually contain glycerin or a vegetable oil or both, often with small amounts of gum tragacanth.

Soaps

In the writer's experience soaps are rather frequently allergenic. Jordan, Walker and Osborne observed two cases reacting to soaps by patch test, among seventy who had no history of dermatitis or allergic manifestations. We have



Fig. 286.—Soap dermatitis. Involvement of the gluteal area due to the fact that the child's panties were not rinsed free of soap after washing. Positive contact reaction to soap. Cure followed more thorough rinsing of linen.

found in routine patch testing with soap solutions in contact dermatitis, that from 5 to 10 per cent react to one or another of the common brands of toilet soaps. The patient does not usually react to all brands.

Soap, prepared for patch testing, should not be too concentrated, otherwise it will be nonspecifically irritant. It is best prepared by making a light solution of soapsuds. We have observed positive reactions to the soaps themselves, with negative reactions to the soap oils obtained therefrom. This is understandable in view of the study of Engman, Moore and Kile who found that among the plant oils the active principle is contained in the unsaponifiable fraction. They observed no reaction to saponifiable fractions.

Men with dermatitis of the face due to shaving soap may solve their difficulties by using electric shavers, dry shavers. The writer has one patient in whom dermatitis was relieved in this way. As pointed out by Shellow, traumatic dermatitis may accompany the use of dry shavers, especially if one fails to properly clean the face beforehand or if one attempts to shave too closely.

A six-year-old child developed angioneurotic edema of the forehead and face following the use of Drene Shampoo. After she had cleared up she slept with her sister who had had a shampoo with Drene that morning. This resulted in recurrence of the edema.

Miscellaneous

Biederman (1936) described contact dermatitis from *ethyl gasoline* vapors. It was not necessary for the gasoline to come into direct contact with the skin.

Templeton and Allington (1937) have reported dermatitis of the face from the *dust of dictaphone cylinders*.

Phenylhydrazine is used in analytic chemistry, the manufacture of dyes, and in medicine. Downing (1937) reports dermatitis from its use in the rubber industry.

CHAPTER LXIX

DIAGNOSIS AND TREATMENT OF CONTACT ALLERGY

Sulzberger writes, "It may be stated that while all reports of new sensitizers are warranted when brief, the general laws governing the contact-eczema type of sensitization are certainly more important than the addition of new specific allergens to the existing list. Recent investigators have continued to emphasize the fact that the patch test, like other skin tests, while *specific* is not necessarily diagnostic. In other words, positive results cannot be regarded as proof absolute of the clinical significance of the substance tested: and negative results do not constitute exoneration. Each test must be evaluated in conjunction with all other factors, such as careful and exhaustive histories, opportunities for exposure, clinical and histologic appearance of the dermatosis, and particularly the results of elimination and renewed exposure."

Specific group reaction.—As in atopy there appears to be some tendency toward group sensitization in contact dermatitis, especially to plant allergens. Thus, Brunsting and Anderson found that patients reacting to ragweed oil not infrequently reacted also to oil derived from burweed marsh elder, turpentine and pyrethrum.

Cutaneous hypersensitive reaction. On the other hand, there appears to be a tendency which is certainly less obviously due to group sensitization, for persons with an allergic exudative dermatitis to react nonspecifically to certain eczematogenic substances. Thus, Grolnick states that adhesive dermatitis occurred more readily in persons manifesting some other form of contact dermatitis. "It would appear that persons with adhesive sensitivity are prone to show sensitivity to other common contact substances, or vice versa." Bloch believed that the eczema patient differed from the noneczema patient in that the former was hypersensitive to certain unrelated eczematogenic substances. Goldman and Pfofi mention this in their discussion of lacquer dermatitis, where they found that the eczema patient reacted four times more frequently to Japanese lacquer than the control case. An etiologic significance often was not established. The point of this discussion is that, as stated by Sulzberger, a positive patch reaction does not necessarily indicate the offending substance.

Site of testing.—The method of application of patch tests has been described in Chapter XXII. Substitutes for adhesive for patients allergic thereto have been discussed under adhesive dermatitis. Mahler has shown that the upper half of the body and flexor surfaces of the extremities are more reactive than other areas. He also found that at normal body temperature profuse perspiration did not affect the results of patch testing. In febrile cases there was a tendency toward nonspecific increase in skin reactivity.

Regional skin response.—According to Sulzberger and Kerr different areas of the skin react in varying degrees to contact factors. Thus if dermatitis involves the face, the best area for patch testing is either the face or the V of the neck. Apparently there is some immunologic relationship between the exposed

areas of the face and of the V of the neck. They have observed negative or nearly negative reactions on the back to contact allergens which caused trouble on the face, while the reactions in the V-shaped exposed area of the neck were positive. They believe that this area is the best for testing in cases of dermatitis of the face. These observations tend to confirm those of others, that certain areas of the skin may be more responsive than others.

The authors also bring out that one may develop contact dermatitis from a substance with which the skin has come into contact for years without previous ill effects. In the study of a case of contact dermatitis, one should not only test for contact allergy with substances new to the skin but also with those with which the skin has been in contact for long periods of time.

Sulzberger and Kerr believe that before a suspicious substance can be completely ruled out as a possible cause of contact dermatitis, the sites of previous eruptions must be tested by contact with that substance. Other portions of the body may fail to react.



Fig. 287.—Carbon tetrachloride dermatitis, in a man engaged in dry cleaning.

Duration of observation. Finally, it should be emphasized that the site of patch testing should be observed, in case of doubt, not just through the 24 or 48 hours of patch contact but through several subsequent days up to a week or longer. Occasionally delayed reactions of this type occur. Positive reactions after 6 or 7 days may indicate commencing sensitization as a result of patch testing and should not be interpreted as indicating a previous excitant.

The exclusion bandage. Shelmire* suggests that when doubt exists concerning the existence of contact dermatitis, a protective Unna boot may be applied and left in place for a week or ten days. This prevents continued

*Shelmire, J. Bedford, Dallas, Texas. Personal communication.

contact in the protected area. Improvement of dermatitis in this area at the termination of the test as compared with dermatitis elsewhere is strong presumptive evidence of a contact factor.

The composition of Unna's paste is as follows:

Zinc Oxide -----	1000 gm.
Gelatin -----	600 gm.
Glycerin -----	1400 cc.
Distilled water -----	2200 cc.

De Takats prefers the following formula:

Zinc Oxide -----	100 gm.
Gelatin -----	200 gm.
Water -----	300 cc.
Glycerin -----	400 cc.

The material is cut into slices and warmed on a water bath before use. The boot is applied to an extremity which is cleaned with soap and water and thoroughly dried. The melted paste, cooled to a temperature tolerated by the skin, is applied with a large brush. Before it has dried it is wrapped in a smoothly applied single layer of gauze bandage. The bandage is not reversed because of danger from wrinkles. The second coat of paste is then applied followed by a second layer of gauze bandage. If more support is required a third layer may be applied.

Shelmire also recommends that the patient with contact dermatitis keep a "contact diary" just as the person with food allergy keeps a food diary. In this way he becomes more conscious of substances with which he establishes contact.

Sulzberger and Rostenberg's Outline

An outline for diagnostic study has been proposed by Sulzberger and Rostenberg on which it would be difficult to improve. The writer therefore quotes this outline verbatim as follows:

The following outline does not pretend to be complete. It is intended to serve only as a rough guide, as a framework upon which to build the more detailed investigative procedures necessary in each specific case. * * * Many important allergic—and some presumably allergic—dermatoses have been but briefly mentioned or deliberately omitted; several of these, because studies have not, as yet, led to procedures of more than limited practical diagnostic and therapeutic usefulness (tuberculids, trichophytids, epidermophytids, moniliids, syphilids, etc.); others, because the nature of the presumptive allergen is, as yet, unknown and routine testing is therefore impossible (infectious eczematoid dermatitis, multiform and nodose erythemas, dermatitis herpetiformis, rheumatic eruptions, purpuras, etc.). While investigative and particularly research work naturally includes skin tests in these dermatoses, their detailed discussion would have extended this summary without, in our opinion, adding materially to its practical value.

Introductory General Data

(Regardless of the type of dermatosis)

1. Name, age, sex, nationality, race, previous illness, personal and family history, etc.
2. Occupation.
3. Hobbies and avocations (sports, games; pets of all kinds, the substances used in their care, and the parasites to which they are subject; photography, etc.).
4. Medicaments (topical and internal).
5. Seasonal incidence, cyclic course, etc.

6. Dietary habits (excesses, iodized salt, etc., deficiencies, vitamins, etc.).
7. Skin qualities and general appearance—dry and fissured, or oily skin; hyperidrosis, etc.
8. Endocrine, vasomotor, and nervous disturbances.

Investigations for the Differential Diagnosis of True Eczema (Contact Dermatitis, Dermatitis Venenata Type) and Eczematoid Dermatoses (Atopic Dermatitis, i.e., Disseminate Neurodermite; and Seborrheic Dermatitis)

A. Clinical appearance of eruption as an aid in differential diagnosis.

1. Distribution and localization of eruption (localized or disseminate, sharply demarcated or not, symmetrical or not; sites of predilection—for example, primarily in exposed areas or not, on seborrheic areas or not, intertriginous or not, on extensor or flexor surfaces, on face, or on feet and on hands).
2. Characteristic or primary efflorescence (polymorphous or not, weeping, lichenification, pigmentation, scaling; papular, vesicular or not [vesicles in eczematous appearing eruptions are almost pathognomonic of true eczema, i.e., contact type dermatitis]).

B. History as an aid in the differential diagnosis.

1. Family and personal history of atopic conditions (hay fever, asthma [not cardiac asthma], infantile eczema); when positive in a case of eczematoid dermatitis, this history speaks in favor of an atopic dermatitis, i.e., disseminate neurodermite.
2. Family and personal history of seborrheic conditions ("kerosé" of Darier, oily skin, seborrheic pityriasis, alopecia, acne, seborrheic dermatitis); these when present in excessive degree speak somewhat in favor of seborrheic "eczematoid" dermatitis.
3. Personal history of eczematous mycoses (dermatophytids) or previous truly eczematous eruptions, i.e., contact type (when present speaks in favor of contact dermatitis).
4. History of occupational, home, and social contacts.
 - (a) Chemical: dyes, metals, caustics, bleaches, detergents, plants, insecticides, lacquers, paints, varnishes, cosmetics, topical remedies (prescribed and proprietary), internal medication, etc.
 - (b) Physical: heat, cold, actinic effects, moisture, friction, and other traumas.
 - (c) Combinations of physical and chemical agents.
5. History of seasonal or periodic occurrence.

Atopic dermatoses often exacerbate seasonally with (in New York) a peak in the autumn and early winter. Seasonal or periodic recurrences may give a clue as to the etiology in certain contact dermatitides, such as plant dermatitis; or in certain cases of vocational or avocational dermatoses. The chronology of recurrences is, for example, of first importance in certain occupational eczemas which improve while the patient is away from certain kinds of work and exacerbate when this work is resumed.

6. Topical remedies previously used (more or less recently).

While this investigation does not help to ascertain the etiology or nature of the original complaint, it is true, nevertheless, that practically all topical remedies, proprietary or prescribed, can sensitize and cause eczematous dermatitis; and in our experience a relatively high percentage of cases of contact dermatitis is due to some remedy applied to the original lesion, which may have been insignificant and often of a different nature from the contact dermatosis which brings the patient to the physician (mercury applied to seborrheic dermatitis or impetigo, local anesthetics applied to itching areas, sulfur to scabies, germicides used in treating cuts, wounds, or as general disinfectants in surgery, etc.). One of us has called attention to the fact that contact dermatitis from local anesthetics may run a very protracted course, the dermatosis and particularly the itching very often persisting many weeks after the last contact with the offending anesthetic. This investigation of the remedies used often brings to light a combination of atopic and contact dermatitis, or more frequently of seborrheic and contact dermatitis.

C. Clinical and laboratory investigations to establish differential diagnosis.

If after the above considerations the differential diagnosis of contact dermatitis, atopic dermatitis, and seborrheic dermatitis is still uncertain or impossible, the following investigative measures are employed:

1. Patch tests with 20 or more standard eczematogenous substances; numerous positives speak in favor of a contact dermatitis.

We employ the following as standard substances for routine patch testing (Table LXX):

TABLE LXX

*Standard Substances for Routine Patch Testing**

Copper sulfate 5% aqueous solution
Turpentine 50% in olive oil
Sodium arsenate 10% aqueous solution
Neo-arsphenamine 0.2% aqueous solution
Milled pyrethrum powder
Butesin picrate 1% in white vaseline
Quinine hydrochloride 1% aqueous solution
Resorcin 10% alcoholic solution
Paraphenylenediamine 2% in white vaseline
Old tuberculin 0.1% saline solution
Oidiomycin 1-10 Lederle
Trichophytin 1-100 Lederle
K I 50% in white vaseline
Formalin 5% aqueous solution
Nickel sulfate 5% aqueous solution
Mercury bichloride 0.1% aqueous solution
Linseed oil
Ammonium fluoride 2% aqueous solution
Anesthesin 5% in white vaseline
Potassium dichromate 0.5% aqueous
Novocain 1% aqueous solution
Mercurochrome standard solution
Orris root (powder)
Iodoform (powder)
Para red, deep (powder)
Para red, light (powder)
Sudan III 5% in mineral oil
Methyl orange 5% aqueous solution
Rhus toxicodendron (13% solids), 0.02% in acetone

*This list differs slightly from that of the original article, having been brought up to date by Sulzberger (1939).—W. T. V.

2. Scratch tests or intracutaneous tests with a series of common atopens. (If there are numerous wheal reactions, this speaks in favor of atopic dermatitis.)

3. Blood counts for eosinophilia. (If eosinophiles are markedly increased, it speaks somewhat in favor of atopic dermatitis; if they are not increased, this does not rule out this condition.)

If all the above investigative procedures lead to negative results, seborrheic dermatitis must be more seriously considered as a possible diagnosis. If number (1) is positive and numbers (2) and (3) are negative, the combined evidence would favor the diagnosis of contact dermatitis. If, vice versa, number (1) is negative and numbers (2) and (3) are positive, this speaks for atopic dermatitis. While if numbers (1), (2), and (3) are positive, the result suggests a possible combination of contact eczema and atopic dermatitis.

(The diagnostic measures discussed apply to some extent to the differential diagnosis between infantile eczemas of the atopic, seborrheic, and contact types.)

Investigation of True Eczema, i.e., a Proved Case of Contact Dermatitis (Dermatitis Venenata) in Order to Determine the Specific Etiology

A. The localization of the first appearance, or the site of predilection of the eruption directs attention to certain substances.

In general the face and scalp are first affected from hair dyes, cosmetics, etc.; neck and face are first affected from furs, fur dyes, collars, scarves, necklaces, etc.; hands and forearms are first affected from occupational substances, gloves, soaps, cleansers, etc.; the torso is first affected from rayon, silk, wool, clothing in general, rubber girdles, substances used in massaging, bath salts, etc.; feet and legs are first affected from shoe leather, shoe polishes, sock finishers, sock dyes, etc.; ring fingers, wrist, garter buckle areas, and lobes of the ears are first affected from metal, bakelite, celluloid, etc.; spectacle areas from metal or artificial tortoise shell; and so on, for a list infinitely long.

B. The occupation of the patient directs attention to certain substances.

For this investigation, it is necessary to know or to become acquainted with the multitudinous eczematogenous substances which represent the different hazards in different occupations. . . . Common industrial causes of contact eczema are the following: dyes, bleaches, soaps, detergents, lacquers, paints and finishes, turpentine, plants, woods, glue, rubber and vulcanizers, cement, flour, spices, yeasts, metals and metal polishes, quinine, formalin, and other chemicals, celluloid and bakelite, and all the innumerable substances connected with the manufacture and finishing of synthetic and natural products.

C. The patient's hobbies direct attention to certain substances.

Here again, space permits the mention of only a few examples: in the case of horse-men—leather and leather polishes, materials used in cleansing and disinfecting stables, etc.; in the golfer—plants and grasses, the leather and wood of golf clubs, the golf gloves, club polishes, taped handles, etc.; in the hunter—plants and grasses, gun oil and gun polishes, etc.; in the amateur photographer—the chemicals used; in the mah jong player—lacquered tile; in the violinist—rosin, chin rest, wood, or wood finish. In the case of patients having pet animals, not only the animals' hair but also the substances employed in their care and cleanliness are to be considered.

D. The investigation of practically ubiquitous causes.

Once again, the list is incalculably long. In practically all women, the ingredients of cosmetics, such as orris root, perfumes, soaps, mascara, coloring materials, hair and lash dyes, face creams, massage creams, wave-set and other lotions, are suspect; and in practically all men, shaving materials, soaps, hair lotions, brilliantine, etc.; and in all children, all toys. In persons of all ages, shoes, socks or stockings, their dyes and finishes, hatbands, wrist watch straps, garters, nickel (coins, etc.) must be considered. In practically all homes, soaps, insecticides, disinfectants, floor and furniture polishes, anti-moth preparations, plants, phenol and formalin derivatives, bakelite, rubber and its accelerators, etc., are suspect. Contact with printer's ink and rotogravure colors is almost universal. (It is here necessary to consider not only the substances used by the patient but also those used by others in the patient's environment—see F in this group.)

E. Furthermore, as specifically mentioned under I, B, 6, all remedies used in previous treatment are suspect and must be applied as patch tests. Moreover, although rarely, certain eruptions of true eczematous (contact type) dermatitis can be caused by ingestion and the hematogenous distribution of the causative agent. The best examples of this are the eczematous eruptions due to quinine, to urotropin (formaldehyde), etc.

F. Substances used by persons in the patient's environment.

In the search for possible causative agents, the dyes, topical remedies, cosmetics, etc., used by others in the patient's environment must be considered. We have seen, for example, a case of contact dermatitis in a husband, caused by an antipruritic lotion used by the wife, and two instances in which a mother had contact dermatitis from washing the clothes of a child who had been using a proprietary antipruritic ointment.

G. Fungi of various genera can cause epidermal hypersensitivity and eruptions of contact dermatitis type (eczematous and dyshidrotic "ids"). It is quite possible that other microorganisms can cause similar dermatoses (Bruno Bloch's "microbids," and "bacterids" of Darier). Unfortunately, a detailed discussion of these eruptions would prove too lengthy for this brief outline. Such etiologies, however, must be considered either as the direct cause of the dermatitis under investigation, or as contributory factors by causing an original eczematous sensitization to fungus products with ensuing polyvalence to include contact substances, or as complicating factors of a contact dermatitis originally caused by non-living agents. Sensitizations of the epidermis to the products of microorganisms, i.e., eczematous "ids," are here not differentiated from contact dermatitis; from an immunologic standpoint, the pathogenesis seems analogous if not identical.

Rostenberg and Sulzberger (1937) call attention to the fact that patients with contact dermatitis are likely to react to patch tests with many different substances. "Regardless of whether one construes these multiple positive reactions as a manifestation of a nonspecific skin irritability, or as a polyvalent specific cutaneous reactivity, it is a fact that this phenomenon constitutes a differential diagnostic measure. A patient in whom a series of routine patch tests elicits many positive reactions, is more likely to be suffering from contact

dermatitis than is one who exhibits negative reactions to all such tests. They find this tendency to multiple reactivity high in dermatitis venenata, low in dermatitis medicamentosa, and intermediate in other dermatoses. The conditions in order of frequency of polyvalent sensitivity are as follows: dermatitis venenata, occupational dermatitis, erythema multiforme, seborrheic eczema, infantile eczema, atopic dermatitis, urticaria, dermatophytosis, dermatitis medicamentosa. Soaps in particular are likely to be irritant to those with contact dermatitis, less so to those with atopic dermatitis, and usually not at all for those with noneczematous eruptions."

This observation of polyvalent reactivity makes the use of a routine series of tests such as those recommended by Sulzberger and Rostenberg logical even though the patient may not be actually having exposure to all of them. If several produce positive patch reactions irrespective of occupational or other exposure or contact, it becomes more probable that one is dealing with contact dermatitis.

TABLE LXXI.—MAYER'S CLASSES OF SUBSTANCES WHICH CAUSE SENSITIZATION DERMATITIS OF ECZEMATOUS TYPE*

(1)	Solid insoluble substances, such as textiles, leather, parts of plants, etc.
(2)	Artificial fertilizers
(3)	Washing materials, such as patent powders, bleaches, etc.
(4)	Oils, shellacs, solvents, etc.
(5)	Acids and alkalis
(6)	Woods
(7)	Flour bleaches
(8)	Aromatic oils
(9)	Alkaloids, etc.
(10)	Other drugs and medicaments
(11)	Soaps
(12)	Shoe-polishes and shoe dyes
(13)	Other dyes and chemicals, such as aniline dyes and photographic developers, paints, etc.
(14)	Reagents [laboratory]
(15)	Disinfectants [insecticides]
(16)	Cosmetics and toilet preparations [face powders, perfumes, toothpastes, etc.]
(17)	Inorganic salts

*Wise and Sulzberger, *Am. Med.* 28: 4, 1933.

Dermatoses of the Ear

Dermatitis in or behind the external ear is observed so frequently in the writer's experience that it merits special discussion. It may be due to seborrheic dermatitis, fungus infection, psoriasis, streptococcus infection of the skin, impetigo, or contact allergy (nickel, feathers, hair dyes, toilet water, shampoos, etc.). The contact agent can usually be determined by patch tests. So-called silver and white gold spectacles may cause nickel dermatitis. Contact with feather pillows may cause eczema on or behind the ear, in warm moist contact areas. Mitchell (1937) has emphasized the importance of low-grade skin infection with hemolytic or nonhemolytic streptococci. Objectively this and the other forms mentioned above can scarcely be distinguished. Testing, microscopic examination and culture are usually necessary.

Lesions usually commence as fissures deep in the retro-auricular fold. Weeping occurs, followed by crusting. The lesion may extend into the scalp. Streptococcus infection may involve one or both ears and may occur secondary to middle ear infection or as a primary lesion. It may involve the external canal and cavum or the retro-auricular region.



Fig. 288.—Impetigo of the ear in a boy also allergic to egg. Before cure was achieved it was necessary for him both to avoid egg and receive local treatment. This illustrates possible interaction between infection and allergy.



Fig. 289.—Dermatoses of the ear. Conditions requiring consideration are, especially, infection (streptococcus, impetigo), seborrheic dermatitis, psoriasis, fungus infection, and contact dermatitis, such as from nickel spectacle frame, feather pillows, telephone earpieces, etc.

Fungi may be identified by microscopic examination of scales in sodium or potassium hydroxide solution. Streptococci may be identified in exuded serum spread on a slide, fixed with heat and stained with methylene blue. Sometimes they may be identified in squamous cells, provided they are sufficiently spread and pressed on the slide prior to staining. Cultures for streptococci may be made by streaking blood agar plates. This is not altogether satisfactory since staphylococci are apt to overgrow streptococci. The latter are usually found only at the tail end of a long, repeatedly zig-zag streak. The addition of 0.06 per cent thallium nitrate or 1/100,000 crystal violet inhibits the staphylococci, permitting streptococci to grow more abundantly. In liquid culture crystal violet, 1/500,000 may be used. Since it is decomposed on autoclaving, it should be added at the time of inoculation of the tube. Mitchell recommends cultivation in brain broth glucose medium, in tubes at least twelve inches long. Crystal violet may be added if desired. Subcultures should be made after 17 hours.



Fig. 290.—Impetigo in an atopic child. Infection of this type usually clears up more rapidly if the allergy is also controlled.

Sabouraud remarked that the streptococcus loves the folds of the skin. Simultaneous involvement may therefore occur as cracks in the nares, along the margins of the eyelids, dermatitis beneath the breast and in other folds and in the umbilicus. Fungus infection and psoriasis sometimes have a similar distribution.

Streptococcus infection usually responds to ammoniated mercury ointment. Seborrheic dermatitis may be treated with salicylic acid and sulfur ointment. Contact dermatitis of the ears should be treated by avoidance. Fungus infection usually responds to salicylic and benzoic acid preparations such as Whitfield's ointment.

Treatment. The treatment of contact dermatitis consists primarily in avoidance and the substitution if necessary of other contact substances to

which the patient is not sensitized. It should be borne in mind that he may later become sensitized to these also. Where sensitization is to plant oil and avoidance is impossible, prophylactic and therapeutic desensitization with oil extract may be tried and has been found efficacious in many cases.

Symptomatic treatment with accepted dermatologic applications will often hasten recovery, provided one realizes the possibility of sensitization to constituents of ointments, etc., and takes proper precautions to avoid the prescription of substances allergenic to the individual.

Industrial Dermatoses

It seems probable that allergic manifestations will become increasingly important in industrial medicine. Allergy in industrial dermatoses has already become a factor for serious consideration. Since there are few occupations in which inhalant allergy might play a part, we may anticipate that it will continue of secondary importance.



Fig. 291.—Contact dermatitis. Differentiation from epidermophytid may be difficult.

Foerster (1936) states that 2 per cent of disabling industrial injuries and diseases fall in the category of disease rather than injury. About 1.5 per cent of total disability is due to dermatoses. Sixty-eight per cent of the total number of occupational diseases in one survey consisted of dermatoses. Schwartz (1935) concludes that more than 1 per cent of workers engaged in basic industries are annually affected by dermatoses. The incidence is much higher in some industries than in others. In general the newer the industry and the newer the chemical compounds, the greater will be the number of cases of dermatitis, due to unanticipated hazards, lack of protective measures, and lack of adaptation on the part of the worker.

Foerster states that allergy plays a predominant role in industrial dermatology and accounts for some of the most difficult problems in this field. No statistics are available on the relative frequency of allergic dermatoses as compared with other industrial dermatoses but the proportion is probably high.

Lane (1936) states that 38 per cent of a series of occupational skin disease caused disability lasting from 2 to 4 weeks; 21 per cent from 1 to 3 months; 16 per cent from 3 to 6 months and 24 per cent, more than 6 months. In another series 69 per cent were disabled for at least 2 weeks while in a third, 335 persons were disabled for a total of 5,685 weeks, an average of 15 weeks per person.

Sulzberger states that occupational dermatoses constitute over 65 per cent of all industrial disease and that the estimated loss per annum in the United States is over four million dollars. Comparable figures hold in Overton's survey for England.



Fig. 292.—Trichophytids. Differentiation from contact dermatitis and local infection is often difficult.

The allergic factor.—Wise and Sulzberger (1933) have discussed the allergic aspects. They bring out that one of the most confusing factors, when present, is fungus infection of the ringworm type. The familiar secondary dermatophytid may be identical in symptomatology, location, clinical and histologic appearance with contact dermatitis. It is sometimes impossible to distinguish between contact eczema and "id." They give the following reasons.

1. A large "id" may originate from an original focus so small as to be scarcely recognizable. It may be no more than a slightly discolored, pinhead sized roughness of a toenail.

2. Most persons in this country have such foci, usually in the toenails or in the interdigital tissues. Their presence therefore does not necessarily prove that the local lesion on the hand is due to the fungus infection.

3. The majority of dermatophytids affect those areas in which occupational dermatoses usually occur, namely, the hands.

4. Microscopic examination of the lesion does not aid in differentiation, since "ids" are usually sterile, no fungi being recovered therefrom.

5. Positive skin reactions to trichophyton and monilia albicans extract are so common (75 per cent of adults investigated in New York City) that this test is of little or no value in differential diagnosis.

Still further complicating the issue is the apparent fact that persons with fungus sensitization become predisposed to additional skin sensitization to other nonrelated allergens. We have discussed this elsewhere as applied to fungus and bacterial sensitization in arsphenamine allergy. This fact has also been brought out by White and Taub (1932) and by Osborne and Putnam (1932).

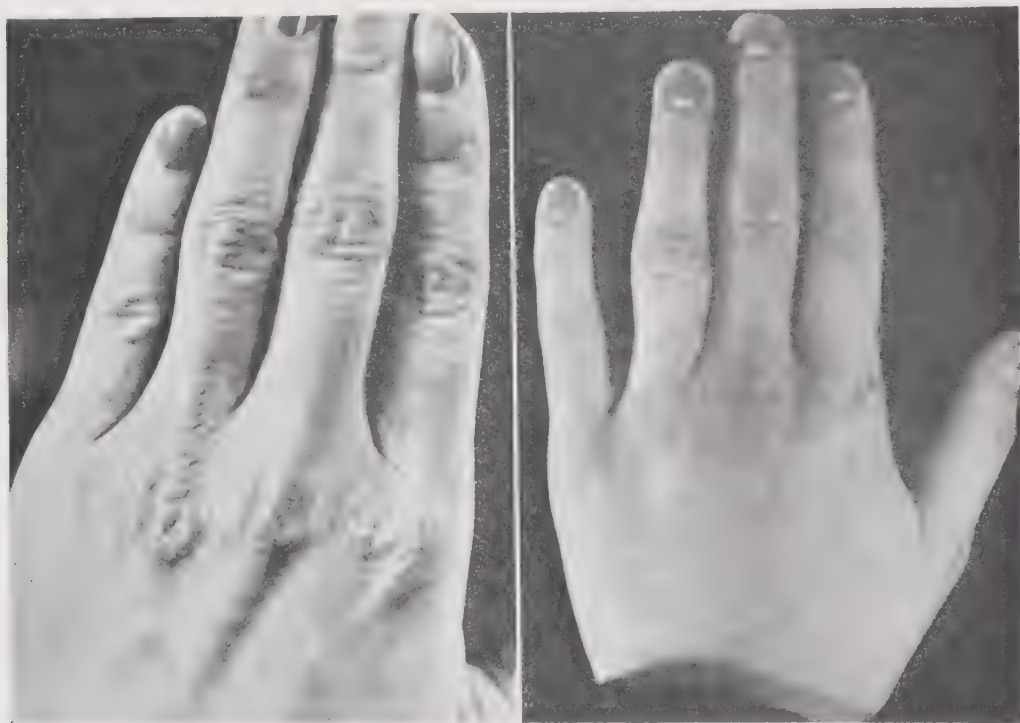


Fig. 293.—Trichophytid. This may occur anywhere but especially on the upper extremities. It may resemble a variety of other local conditions such as psoriasis (left), low-grade cellulitis (right), and must sometimes be diagnosed by a process of exclusion.

Factors which predispose in allergic dermatoses include occupational hazards in which there are frequent skin traumata; occupations involving an excess of heat and moisture; occupations which render the skin excessively dry. Undoubtedly a most important factor is the nature of the materials handled. Certain drugs and other materials are much more highly allergenic than others. Thus, 60 per cent of employees working with paraphenylenediamine in fur dyeing plants in Leipzig suffer from sensitization to the dye and about one-third of the entire pay roll is constantly on the sick list.

On the whole, industrial compensation laws dealing with allergy are inadequate and at times ambiguous. The medicolegal difficulties in the United States have been discussed by Wise and Sulzberger (1932), Parlato (1934), Sulzberger (1935), Downing, Lane and Foerster (1936). Mumford (1934), discussing the problem in England, suggests the organization of panels of consulting dermatologists to pass on individual cases. Bernard (1934) points to the need for revision of the Belgian compensation acts.

TABLE LXXII.—CRITERIA FOR DIAGNOSIS OF OCCUPATIONAL SKIN DISEASE*

DEFINITE	PROBABLE	POSSIBLE	NEGATIVE
<i>History</i>			
Exposure or injury	Relation less clear cut	Discrepancies in story	Definite evidence of other skin disease
Attacks—on exposure	Substances less often cause irritation	Substances seldom irritate	
Amelioration—on stopping work			
No outside source of irritation		Other possible irritant	Definite relation to outside irritant
<i>Examination</i>			
Lesions consistent with exposure	Lesions less characteristic	Lesions more indefinite	
Location—consistent	Exam. late	Other possible diagnosis	
No evidence of other skin disease	Condition nearly well		

*Lane, C. Guy: *New England J. M.*, 215: 859, 1936.

Sulzberger lists imperfections in the compensation laws.

1. Limitation of compensation to certain specified dermatologic entities. If certain skin diseases are indicated by name, others which are equally occupational are often omitted.
2. Limitation of compensation to dermatologic entities caused by certain specified substances. Unfortunately other substances not specified may cause the same type of skin reaction.
3. Specification of trades and occupations which shall be entitled to receive compensation by a listing of so-called hazardous occupations. This leads to the limitation of compensation to certain industries, trades, occupations and to the exclusion of all others.
4. Limitation of compensation to those cases in which the occupation is a proved cause. Often proof is difficult. Often the occupation is not the sole cause but is contributory. This applies, for example, in fungus infections, discussed above.
5. Award of compensation without proof of the causal connection between the occupation and the existing dermatosis. This works injustice upon employers and insurance carriers. Figley, for example, has reported the case of a man who for eight years received compensation for a dermatitis thought to be due to a sensitization to an industrial oil, before it was found that his disability was due to allergy to silk, house dust and certain other allergens.

Sulzberger suggests that a general law, worded approximately as follows, would circumvent the majority of difficulties.

“When an employee suffers from any skin condition, or from the sequelae of any skin condition, in which his occupation can be proved, beyond reasonable doubt, to be directly or indirectly a causal or contributory factor, such employee is entitled to compensation commensurate with (a) the degree to which the occupation is responsible for the skin disease and/or its sequelae; and (b) the extent and duration of the skin condition and/or sequelae, the resulting discomfort, disability, and/or disfigurement. Such employee is further entitled to the payment of the reasonable costs of adequate medical attention and treatment, administered through qualified physicians, hospitals, etc., of his own choice; and such employee is further entitled to such reasonable costs of investigation, and of expert testimony as may be necessary in order to substantiate his claim.”

Downing remarks that if an untrained worker suffers an incapacitating dermatitis from an occasional occupation and then returns to this job when other work is available, it would seem that he has ulterior motives. Industry

should not be compelled to pay compensation merely because an individual is unfit to perform certain types of work. The problem, however, becomes quite different with the skilled artisan who finds himself no longer able to continue with a type of work in which he has spent years perfecting his technic.

In the prevention and treatment of industrial dermatoses in general, Wise and Sulzberger emphasize several points. Trained artisans often find it necessary to continue with their work even though experiencing illness therefrom. The shoemaker must often continue to work with leather. Other



Fig. 294.—Contact dermatitis. Differentiation from trichophytid and psoriasis is important.

persons continue at work, with ulterior motives, in the hope of obtaining compensation, and must be recognized as malingerers. Poverty often precludes adequate treatment or change of occupation.

These authors emphasize the importance of the patch test in diagnosis, as well as exposure of the patient to conditions identical with those suspected as causing the dermatosis. They suggest that in industries in which the materials handled are known to be highly allergenic, employees should be tested by patch test with a series of 20 or more standard "irritants" to determine whether they have a "tendency toward eczematous hypersensitivity in gen-



Fig. 295.—Seborrheic eczema. Differentiation from atopic and contact dermatitis is often difficult, especially in children.



Fig. 296.—Contact dermatitis from a silk scarf. The location of the lesion on the skin often suggests the possible excitant.

eral." Such persons should be weeded out since it is probable that they will develop industrial sensitization. Conversely, materials used in industry which are known to be strongly eczematogenous should be discontinued unless they are absolutely essential adjuncts to the industry. Not infrequently other materials less highly allergenic can be substituted for the same use. They stress the need for the establishment of an institution devoted to industrial diseases. Much of this work is already being done by governmental agencies, many important contributions having been made, especially by Schwartz.

Discussion. The preceding summary of the problems of industrial allergic dermatoses provides a general idea of the problem. Omitting any consideration of malingerers, the two simple facts that must be weighed are (a) that the occupation is responsible for the disease and (b) that the disease would not have occurred had the individual not been predisposed. Leaving aside the factor of negligence in failure to provide adequate safeguards and in the use of highly allergenic chemicals, a fine point is raised as to how much responsibility the employer must assume for a constitutional predisposition in the employee. One cannot criticize an employee for believing that he should be compensated for an illness acquired incident to his occupation after having entered the occupation free from disease.

Another problem arises when the employee has other allergic diseases not associated with his occupation. For example, a middle-aged man who had had frequent and severe asthma up to about age 20 was employed in an automobile assembly plant, working in the paint division. He developed severe dermatitis. After a month's vacation he was nearly cured and returned to work. Dermatitis recurred, this time with asthma. He was then permanently discharged but the dermatitis and asthma persisted. When seen by the writer two years later he was found allergic to house dust and several foods and gave positive patch reactions to constituents of the paint. He had been unable to work during the intervening two years.

The question arises whether his asthma would have recurred had his allergic balance not been disturbed by the development of contact dermatitis. How much of his illness should properly be construed compensable due to occupational hazards, in view of the fact that (a) both symptoms were inaugurated by occupational exposure, (b) a known predisposition existed, (c) symptoms persisted far too long after discontinuance of work to be considered as still due to exposure to paint? Other excitants continued active but they were excitants to which he had previously been exposed without symptoms.

Fortunately decision as to compensability rests not with the physician but with the courts. Complicated problems such as that illustrated above require a nicety in judgment to prevent miscarriage of justice on either side. Sulzberger's recommendations cited above, are, I believe, adequate as general principles. Many individual problems will require much serious consideration. This is a new phase of legal medicine which must be carefully worked out in the next few years. The appropriate time for the solution of the problem is the present, when claims for industrial allergic disability amount as yet to little more than about one-half of one per cent of all disability claims.

It will be the duty of the allergist to provide industrial boards with adequate information and advice, given from the point of view of employer and employee, as an aid in the establishment of adequate precedents.*

*A very comprehensive symposium on Industrial Dermatoses, contributed by the various dermatologists mentioned in this discussion, appeared in the *J. A. M. A.*, Oct. 22, 1938.

PART XIV

PHYSICAL ALLERGY

How does cold act? I believe in three ways. First: As a local irritant, just as damp or fog acts, the cold inspired air at once producing the bronchial spasm. Second: As a stimulant to the cutaneous surface, acting reflexly via the centripetal spinal nerves. In no other way do I conceive we can explain the immediate production of asthma by cold to the feet, &c. Third: By producing catarrhal bronchitis. In the first two cases the cold acts at once; in the last remotely, not perhaps for days. In the first two a certain amount of cold inevitably produces the asthma; in the last it entirely depends on whether it gives rise to "a cold"; if not, the greatest depression of temperature may be endured without the slightest injury.

How do heat and thunder act? I believe by producing greater general irritability of the nervous system, and making it more sensitive to sources of disturbance of any kind whatever.

—HENRY HYDE SALTER

CHAPTER LXX

PHYSICAL ALLERGY

The findings of Duke, Horton, Brown and Roth, Swineford and others have been discussed in the chapter on Diagnostic Technic in Physical Allergy.

There can be no doubt of the existence of the phenomenon which Duke designates as physical allergy or sensitiveness to heat, effort, sunlight, and cold. That this is not an atopic disease is indicated by failure to achieve positive results by passive transfer.

Difficulties.—Failure of many to recognize the syndrome when it exists is undoubtedly due to the complexity and interplay of the etiologic factors. The uncomplicated case should be relatively simple: the person who develops asthma when exposed to cold or urticaria when exposed to heat or light. But, as brought out by Duke, the problem is much more involved in many cases. Some react to heat, cold or effort within a few minutes, others not until several hours afterwards. The latter are more difficult to recognize. Some heat cases react throughout the year, others only at certain seasons. The situation is similar with cold allergies. Some heat allergies adjust themselves satisfactorily to degrees of heat and react only when they have been previously

chilled. Under these conditions they will react to a degree of heat to which they would not otherwise respond. Some cold allergies react only in the winter; others only in the summer, responding to a fall in temperature to which they would not react in winter.

To further complicate this situation, some react to heat only when simultaneously exposed to cold. This implies testing with heat by external application while the patient is breathing cold air, or testing by inhalation of warm air while the patient is in a cold room. Humidity also may play a part.

This fact, that the patient may react only to certain combinations or sequences of heat, cold, effort and atmospheric conditions, makes it extremely difficult at times to trace down the etiologic factors. It may make the patient's behavior appear extremely inconsistent. As stated by Duke, "The fact is, however, that these patients are extremely consistent in their reactions, in fact so consistent that they often appear inconsistent. They can be understood only after careful study and are then found to react consistently to the conditions of heat, effort or cold to which they happen to be sensitive."

Hyperergy—effort syndrome.—According to Duke the familiar symptom complex known as *effort syndrome* or *soldiers' heart* is often due to sensitiveness to heat. The symptoms, tachycardia, easy exhaustion, weakness, dizziness, tremor, fainting spells, feeling of oppression in the chest, anorexia, nausea, may follow physical or mental effort or exposure to heat. In the normal daily routine these persons adjust themselves within their limitations. When exposed to the standardized routine of army training these limitations are exceeded and they develop effort syndrome. Such persons do not tolerate the degrees of heat, mental and physical effort which cause no symptoms on the average person. Duke believes that many cases of heat prostration and syncope are due to similar causes; either a single factor, particularly heat, or, more often, the triad of all three. In effort syndrome he reproduces many or all of the above symptoms by having the patient immerse hands and forearms in a water bath at 42 degrees centigrade. Since tourniquets above the immersed areas do not modify the reaction, Duke suggests that they may be reacting not so much to heat as to the sense of heat. He also finds persons in whom effort syndrome can be reproduced by exposure to cold.

Allergy.—The next classification comprises those who develop typically allergic symptoms such as rhinorrhea, "sinus headache," asthma and urticaria. Where the condition is more chronic the manifestations correspond, the skin symptoms partaking more of the nature of a chronic dermatitis, with dry cracked skin, often with desquamation, sometimes with an actual ichthyosis. These patients usually show wide oscillations in body temperature. They do not sweat. The temperature range is often subnormal.

Normal acclimatization.—Victims of physical allergy often find it difficult to acclimatize themselves to changes of season or changes of location. Normal persons tolerate surprising variations in temperature and humidity. Change of residence from the temperate zone to the tropics usually requires some acclimatization, after which the normal individual tolerates the new conditions without symptoms. But until this is accomplished, he reacts to degrees of muscular effort or even to mental effort, which would have failed to produce symptoms in the temperate climate. The first few days of a change of season from hot to cold or cold to hot are felt by most persons much more keenly than are much more pronounced degrees of cold or heat later in the season. But the normal person becomes acclimated and symptoms do not persist.

Failure of acclimatization.—The victim of physical allergy, reactive to heat, may acclimate himself sufficiently in the summer so that he has no symptoms at that time. But when acclimated to the cold of winter he may find himself unable to adjust himself rapidly to a sudden change of temperature at that time, such as going into an overheated house. In this way a heat allergic may have symptoms only in the winter time.

Some cold allergies react only during the coldest days of winter. Others react chiefly in the summer. In the latter Duke finds that they react to cold most markedly after exposure to heat. The rubbing of ice on the skin causes no symptoms unless the skin has just been exposed to the heat of a lamp. These patients often tolerate cold better in midwinter than at the beginning of the season.

Some persons reactive to heat and effort have symptoms only when breathing cold air. They do not have symptoms in the summer when the air is warm. They have symptoms from even less degrees of heat or effort in the winter, when breathing cold air. In the winter they tolerate effort better indoors than outdoors. Such a patient may have asthma if he sleeps in a cold room and uses an excess of cover but may remain free when sleeping in a warm room with little cover. Some cold allergies have attacks following cold baths in the summer, with the body exposed to cold, but breathing warm air. Cold baths in the winter may cause no symptoms in these cases.

Care in testing.—Duke states that early in his studies he learned to his regret that when testing, one must counteract the effect of the provocative factor. Following the production of an attack either with heat or cold, the patients are likely to develop acute respiratory infections unless the reaction is promptly controlled by the application of the reverse effect. Having produced a reaction with heat, cold should be applied to control the reaction even though it be relatively mild, and vice versa.

He believes that the tendency to repeated head colds or even pneumonia with change of season may be associated with allergy to heat or cold. Therefore, in the study of this type of case one should inquire concerning frequent head colds and the season of the year in which they usually occur.

Pathogenesis.—With regard to the pathogenesis of physical allergy, Duke remarks that a frequent cause, especially in young people, is an acute febrile disease which might presumably disturb the heat regulating mechanism of the body. He has also seen it follow trauma to organs which play an important part in the regulation of body temperature: fracture of the skull, cerebral hemorrhage, lightning stroke. Cardiac or vascular diseases which impair circulation; endocrine diseases (adrenals, pituitary or thyroid); disease of the intestinal tract which alters the absorption of protein; or disease which interferes with normal surface moisture, such as ichthyosis may be etiologic or complicating factors.

As evidence of disturbance of the heat regulating mechanism Duke points out that the body temperature is almost always subnormal, sometimes as low as 92° F., and decidedly unstable, with wide variations from exposure to changes of temperature that should cause no variation in the normal individual. The metabolic rate is unstable, often low, sometimes slightly above normal and tends to fluctuate with changes in surface temperature. In one case it was minus 60 even though there were no symptoms of myxedema. Many heat allergies are hyperesthetic to cold and vice versa.

Bray states, "It has been shown that histamine is liberated in the skin of normal people when the temperature of the skin is decreased to 20° F. (minus 6° C.)." In a case of cold allergy he found this threshold for histamine liberation raised 25° F. His patient reacted at 45°. Saylor and Wright observed a case in which the threshold was raised 60.2° F., from 20° to 80.2° F.

Diagnosis.—This review of the phenomena of physical allergy brings out some of the difficulties encountered in diagnosis. Duke has provided a questionnaire which will often be of aid.

Questionnaire Which May Be Used for the Detection of Heat and Effort Sensitiveness and Cold Sensitiveness

1. What is the effect of heat on the skin or of getting hot? What is the effect of mental effort? Physical effort?
2. Is the symptom, caused by heat or effort, relieved by cold or quiet?
3. Is heat or effort more productive of evil in hot weather or cold weather or augmented by the effect of breathing cold air?
4. Is the effect of heat and effort more pronounced after periods of quiet, rest, or depression, or after being chilled?
5. What is the effect of cold on the skin or of being chilled?
6. Is the effect of cold relieved by the effect of heat or effort?
7. Is the effect of cold more pronounced in summer or winter or aggravated by the effect of breathing moist air?
8. Is the effect of cold or quiet more pronounced after marked activity or after being overheated?
9. Is patient affected in like manner by both heat or effort and by cold?

Treatment.—Treatment is at times even more difficult than diagnosis. The mild case is often relieved simply by the avoidance of those situations that have been found productive of symptoms. The highly allergic patient sometimes finds it impossible to avoid them. For these, whether they react to heat or cold, Duke has found that therapeutic alternation of the extremes of temperature may increase tolerance to a high degree. The person highly allergic to heat frequently cannot tolerate exposure to a 1500 watt lamp and the treatment must be begun with a hot water bottle or a small bulb at some distance. As soon as the patient commences to react, cold is applied. When symptoms are relieved heat is again applied. This is alternated several times at each treatment. The degree and duration of heat exposure are gradually increased, until the patient can tolerate, if possible, prolonged exposure to the heat of a 1500 watt lamp. For cold, the reverse procedure is applied. Treatment of effort sensitiveness is applied with graduated exercises and often also with alternating heat and cold.

Duke states that the treatment of cold allergy is easier than that of heat. Cold should not be applied to the point of having the patient shiver. Treatment in all cases should be given daily. After tolerance has been built up it is maintained by daily hot or cold baths.

According to Duke the most difficult cases to treat are those who react to effort while breathing cold air. Treatment is unsatisfactory. The patient should avoid the situation insofar as possible.

Swineford and Weinberg report a case of extreme reactivity to heat in an asthmatic who would experience a severe attack of asthma within one minute after the application of a hot water bottle to the chest. Relief as quickly followed the application of an ice cap or rubbing with ice. They

undertook special means to rule out the factor of suggestion and feel that this was satisfactorily done. They finally achieved a satisfactory degree of relief following intravenous typhoid therapy.

Caven has reported benefit from diathermy in a case reactive to heat and effort. A woman experienced angioneurotic edema after brisk walking, dancing, washing in hot water, sitting in front of a fire, or even meeting strangers. Following moderate heating the swelling would come on within half an hour; within ten minutes after strenuous exertion in hot weather. It usually lasted until she had had a night's rest. In the winter she used more bed clothes than the average; in the summer, fewer.

The condition was produced experimentally by immersion of the hands in hot water and by sitting in front of the fire. Caven tried various remedies without success, including subcutaneous typhoid (without resulting fever), thyroid and pituitary extracts, and hot baths. He then applied diathermy, running the rectal temperature to 102.6° at the first treatment. Treatments were continued at biweekly intervals, increasing the temperature gradually to 104.6 degrees. Following completion of the treatment the patient went through an unusually hot, humid summer, played tennis, danced, etc., remaining practically free from her symptoms.

Martin has observed a girl, reactive to heat, who develops urticaria of the back when walking on the beach, away from the sun, and on the front of her body when sitting before a grate fire.*

The literature contains more reports of successful desensitization to cold than to heat. Dubbs (1935) reported relief from urticaria due to cold with calcium lactate, 1 gram orally after meals. Its discontinuation was followed by return of urticaria. Adrenalin also gave immediate relief of short duration.

The use of histamine and other therapeutic procedures has been discussed in Ch. XXV, p. 248. Roth and Horton (1937) reported relief following the combined use of histaminase and histamine. The patient on more than fifty occasions had collapsed and fallen to the ground when exposed to cold. He obtained relief by pulling his coat over his head so that he might breathe warmer air. He had had collapse symptoms when swimming. His legs would swell when exposed to cold, rain, snow or damp trouser legs. Hand immersion in water at 8 to 10° C. caused local swelling which persisted for four days. Less persistent symptoms were fall in blood pressure, tachycardia and flushing of the face. The patient received a total of 67 units of histaminase in four and one-half days. One unit is the amount capable of detoxicating 1 mg. of histamine in vitro during 24 hours. Following histaminase the patient received hypodermic injections of histamine. He was satisfactorily relieved.

Saylor and Wright described a case with throbbing headaches and generalized flushing when exposed to cold. Ice cream caused swelling of the throat and lips. Carrying a cold milk bottle against the arm caused local reaction. Symptoms occurred when in swimming. There was no other allergic history except that the subject becomes nauseated and often vomits when eating egg. Food tests were negative.

It was found that the temperature of the surrounding air was not as important as the temperature of substances with which she came in contact. In a room at 22.3° C. there was no reaction, but contact of the skin with a metal cabinet in the same room, with temperature 1.2° C. higher than the room temperature, produced local redness and edema. The cabinet seemed colder

*Martin, Walter B., Norfolk, Va. Personal communication.

since it removed heat from the arm more rapidly than did the air. The arm actually became cooler after it had been in contact with the metal for four minutes.

They found the same general response to induced cold urticaria and to histamine injections. There was no local eosinophilia. Menthol in alcohol applied to the skin caused no reaction. Local anesthesia with 2 per cent novocain reduced the extent of the reaction but did not prevent it. Passive transfer was unsuccessful. Edema fluid from a positive clinical response, injected elsewhere into the skin, caused wheal formation.

A second case, an actress, found it necessary to reach the theatre an hour before each performance, otherwise she was covered with urticaria during the performance. She had experienced collapse and near drowning while swimming.

The second case was not treated. The first was satisfactorily relieved following a series of histamine injections intracutaneously.

Reaction to light.—A quarter of a century ago discussion of light waves centered around the visible spectrum with short waves at the violet end and longer ones at the red. However, there are still shorter, invisible rays, the ultraviolet. Later it was shown that the spectrum could be continued, with increasing shortness of the waves, until the extremely short x-rays and still shorter radium rays were reached. Evidence recently suggests that even beyond radium we will find the cosmic rays.

At the other end of the visible spectrum infrared waves, slightly longer than the red, merge into heat waves. Still farther on, we find short radio and finally long wave radio. These latter are measured in yards rather than microns or angstrom units. Wave lengths represented in the visible spectrum of white light appear beneficial rather than harmful to the animal and vegetable kingdoms. Ultraviolet light is more irritating, as is heat when too intense. The deleterious potentialities of radium, x-ray and short wave radio are common knowledge.

It is important to differentiate between photosensitivity as a result of the use of certain foods or drugs and a true allergic sensitivity to light. Some of those persons allergic to light have reactions from a wide range while others are affected only by a rather narrow spectral region. Prurigo aestivalis, eczema solare, and urticaria photogenica may all belong to the allergic group.

Duke (1923) described a case of urticaria due to the actinic rays of the sun. He mentions a report by Ward (1905) and one by Ochs (1910) of the same condition. There have been several reports since then. Weiss in an analysis of the literature concludes that the fundamental factors in light sensitivity are unknown. Hematoporphyrinemia has been suspected but never found. Experimental hematoporphyrinemia does produce sensitiveness to light. The majority of recorded cases have occurred in women and in some of these the sensitivity to light appears to have been related to disturbances in menstrual function.

Harris and Hoyt found that paramecia survived ultraviolet rays that had traversed a cystine solution, eight times as long as those exposed to the same intensity of ultraviolet, which had passed through a noncystine control solution. Ward found that cystine was the only amino acid with pronounced absorption spectrum in the ultraviolet region. These observations suggested

that cystine present in the skin and epidermal appendages tends by absorption to protect protoplasm from the toxic effect of ultraviolet. Ward suggests that the wearing of heavy woolen clothing protects the Arabs from the effects of the sun's rays because of the cystine content of the wool.

Infrared.—McKinnon has described a man who reacts with vesication to what is usually considered normal exposure to sunlight, in whom it was found that ultraviolet produced normal response, while infrared rays applied with the infrared coil at a distance of 24 inches produced vesicles within twenty minutes. The normal response is with erythema at the end of thirty minutes.

Visible spectrum.—Blum and West have studied a patient with urticaria who reacted in the spectral range between 3,900 and 5,300 angstrom units, that is, to blue and violet light. These observations suggest that even within the range of visible light there may be hypersensitiveness or sensitization to surprisingly narrow wave length bands.

PART XV

PHARMACOLOGY

*O laborum,
Dulce lenimen medicumque, salve,
Rite vocanti*

—HORACE
32D ODE, BOOK 1

CHAPTER LXXI

THE PHARMACOLOGY OF ALLERGY

I. DRUGS WHICH ACT THROUGH THE SYMPATHETIC NERVOUS SYSTEM

Epinephrine—Adrenalin

The active principle of the adrenal medulla was first isolated by Abel who named it epinephrine. It was isolated as a pure crystalline compound by Takamine and by Aldrich (1901) and named adrenalin. Other trade names include adrenin, suprarenin, adrin. It has been synthesized. Adrenal gland extract was first used in the treatment of hay fever and asthma by Solis-Cohen in 1898. It was given orally. Bullova and Kaplan first used the 1:1,000 solution subcutaneously in 1903. When given intravenously, epinephrine stimulates the myoneural junctions of the postganglionic fibers of the sympathetic nerves, thus producing symptoms identical with those of sympathetic stimulation.

Epinephrine raises the arterial blood pressure as a result of peripheral vasoconstriction, the most pronounced reaction being in the splanchnic area. Indeed the effect may be so pronounced in this area as to overcome constriction elsewhere, especially in the muscles, with resulting increased passage of blood through the latter. The smaller veins as well as the arterioles are constricted. This is pronounced in the hepatic venules, as a consequence of which blood accumulates in the liver, which becomes swollen. Plasma escapes from the blood in the liver, resulting in an unusually high red count.

The effect on the coronary vessels is not fully established. Most observers find them dilated, but very small concentrations may cause constriction. The heart is accelerated from stimulation of the terminations of the accelerator nerves. If it becomes too rapid, the heart does not fill during diastole, and the blood output is reduced, with resultant fall in blood pressure. The accelerator activity is sometimes overcome by vagus activity, with secondary slowing of the heart.

Very minute quantities of epinephrine in the cat or dog cause fall in blood pressure, while larger quantities produce vasoconstriction with rise. As an explanation it has been suggested that epinephrine stimulates not only the terminations of the vasoconstrictor nerves but also of the vasodilators

and that the action of the former usually predominates. Another suggestion has been that epinephrine causes dilatation of the capillaries which however is usually overshadowed by arteriolar constriction.

The drug produces relaxation of the muscles of the stomach and intestines with increased tonus of the pyloric, ileocolic and internal anal sphincters. Gall bladder movements are inhibited while those of the gall duct are increased. Uterine activity varies in different animals. In the nonpregnant cat relaxation follows injection, while in the pregnant cat powerful contractions ensue.

Applied locally in the eyes, it causes blanching of the conjunctiva and often dilation of the pupils. It dilates the bronchi by stimulation of the bronch sympathetic fibers and consequent muscular relaxation. Other effects on other organs containing nonstriated muscle and on the secretions are similar to those resulting from sympathetic stimulation except in the case of the sweat glands, which do not respond to adrenalin. Hydrolysis of glycogen in the liver is increased, with resulting increased blood sugar and, at times, glycosuria. Urine secretion is increased as a rule. Injected locally, it produces local vasoconstriction with blanching of the tissues. It is used locally in surgery to stop bleeding.

Adrenalin applied to the unbroken skin is not absorbed and exerts no effect. It is absorbed from mucous surfaces, causing blanching. When taken by mouth this local ischemic response causes some discomfort. It is digested and destroyed in the intestinal tract.

The injection of adrenalin causes a variable increase in the red blood cell count, with an increase in the white count. The latter has been attributed to (1) contraction of the spleen, (2) concentration of the blood, (3) direct stimulation of the bone marrow, (4) redistribution of the formed elements in the blood, (5) expulsion of leukocytes from the lymph nodes. Lucia, Leonard and Falconer (1937) have found that leukocytosis follows the injection of adrenalin even after splenectomy, thus ruling out splenic contraction. Since as a rule immature cells did not enter the circulation it appears that bone marrow stimulation is not a factor. The probable explanation is that of redistribution of cells in the blood. Peripheral vascular and capillary constriction forces those cells which are lying immobile, in contact with the smaller vessel walls, into the axial stream.

Syozi (1937) has determined the epinephrine content of the adrenals of rabbits exhausted on a treadmill, finding no evidence of epinephrine exhaustion.

Uses.—Adrenalin hydrochloride is available in aqueous solution in concentrations 1:10,000, 1:1,000 and 1:100. In the rare instances in which its intravenous use is indicated (anaphylactic shock, intractable asthma), 1:10,000 concentration is preferable, in dosage of 1 cc. given very slowly. It may be repeated as indicated.

For routine use in hypodermic medication 1:1,000 concentration is used. A dose of 0.3 cc. or 5 minims usually relieves allergic symptoms. This may be repeated at frequent intervals. Occasionally as much as 0.5 cc. or even 1 cc. is necessary, especially in conditions such as status asthmaticus in which the patient appears to have lost the ability to respond satisfactorily to adrenalin. In such cases relief may be of no more than twenty minutes' duration. But as a rule a single dose of 0.3 cc. will relieve for from two to four hours.

Adrenalin often effectively relieves migraine if administered early, but must be given in quite large doses such as 0.5 cc. every half hour until the headache is gone or the patient is too inconvenienced with adrenalin action (tremor, tachycardia, nervousness). It usually gives temporary relief in asthma, urticaria, gastrointestinal allergy, hay fever and in some cases of angioneurotic edema. It may be applied in 1:1,000 dilution or more dilute to the conjunctiva or nasal mucosa for relief of local symptoms such as allergic conjunctivitis, positive ophthalmic reaction, allergic coryza.

It may be given prophylactically to prevent constitutional reactions along with injections of allergens such as pollen extract. It may be administered in the same syringe, always drawn up prior to the allergen extract, since in this way the dosage of the latter is more accurate. It should not be mixed with the extract for any long period prior to use since it darkens and loses potency. When adrenalin solution is stored in a rubber stoppered bottle, it gradually turns brownish. During this process its activity diminishes and larger doses must be used. For this reason deteriorated adrenalin solution is not desirable. It is not toxic and causes no deleterious side effects. Rarely, patients find that it fails to give relief in episodic allergy. Rarely, patients appear to be hyperergic, complaining of unpleasant adrenalin symptoms from standard dosage.

Lamson (1938) has described clinical and laboratory findings on 2 chronic asthmatics each of whom had through the years received a total of over 20 gallons of adrenalin 1:1000, hypodermically. No evidence was found to show that epinephrine produced specific harmful effect in these cases.

Slow epinephrine.—Keeney (1938) finds that epinephrine base suspended in peanut oil and given deep, subcutaneously or intramuscularly, exerts slower and more prolonged action than 1:1,000 aqueous solution. It is made up, 2 mg. to the cubic centimeter. Doses of 0.5 to 1 cc. relieve chronic asthmatics for from 8 to 16 hours, in contrast with the 2 to 4 hours' relief obtained from aqueous solution. Both preparations may be used together, the aqueous for immediate response, the oil suspension for prolonged effect.

Preparation of a satisfactory suspension is difficult. The sterilized oil is washed with alcohol to remove excess fatty acids. The epinephrine base powder must be added with rapid agitation, otherwise it forms clumps which are not easily broken up. Supersonic radiation tends to keep the particles in suspension.

Spain, Strauss, and Fuchs advocated epinephrine in gelatine which appears to be slowly absorbed, and avoids the possibility of sensitivity to the oil used in Keeney's preparation.

Adrenalin inhalation.—Graeser and Rowe have recommended the inhalation of 1 per cent adrenalin solution for the relief of asthma. A special nebulizer is used which creates a very fine cloud of vapor. The patient learns by experience to estimate the dosage by the number of inhalations and the number of times the bulb is compressed. The dose varies with different persons and with the severity of the asthma. The patient inhales while the bulb is being squeezed.

Lamson suggests that the addition of from 1 to 3 per cent alcohol helps the volatilizing qualities of 1:100 epinephrine, without injuring it. If 1:100 concentration is irritating to the patient, he suggests dilution with distilled water to 1:300 or 1:400. The patient then increases the number of inhalations.

Abramson suggested the use of glycerin to insure the proper size particles for proper spraying.

Larsen and Nielsen have studied the effectiveness of inhalation of 10 per cent nebulized adrenalin. The solution used contained adrenalin 1 gram, chlorbutanol 90 mg., sodium bisulphite 10 mg., 2/N HCl 0.28 cc., sterile distilled water to make 10 cc.

They used two commercial European nebulizers both of which had been found effective. With the better of the two nebulizers 99 per cent of the drops measured about 1.4 microns in diameter. The largest measured 5.6 microns. The velocity of particles in the cloud of spray at a distance of 9 to 12 cm. from the tube averaged 50 cm. per second. The size of the droplet materially influenced effectiveness. Thus a droplet 14.8 microns in diameter, about twice the diameter of a red blood cell, weighed 1000 times as much as the 1.4 micron droplets mentioned above. The factor of settling out then becomes important. A 1.4 micron droplet falls about 0.006 cm. per second while the larger falls about 0.7 cm. per second and is less likely to enter the bronchial tree. The kinetic energy of the larger droplet prevents its altering its course to enter the larynx during inhalation.

Having established these facts, they searched for evidence of absorption through the pulmonary alveoli. When an efficient nebulizer was used, systemic evidence of absorption (blood sugar, blood pressure and pulse rate) appeared almost immediately, within so short a time that absorption must have taken place through the alveoli. With ineffective nebulizers these symptoms did not appear for 40 minutes and were ascribed to absorption through the gastric mucosa.

They found that the inhalation of 1.5 mg. of adrenalin produced pronounced and immediate absorptive effect. Less than 1 mg. produced no evidence of alveolar absorption. They conclude that since 1 mg. does not influence blood pressure, etc., and usually does relieve asthma, this is a safe dose for inhalation. This corresponds to 0.1 cc. of 1:100 adrenalin. One mg. may be inhaled hourly without inconvenience. Nielsen reports that patients received 0.05 mg. every 5 minutes for four times without inconvenience.

Question has been raised concerning the possibility of deleterious effects from local contact of adrenalin on the mucous membranes in such high concentration as 1:100. Local mucosal ulceration and tracheitis have been described. On the other hand, Nielsen recommends as high as 10 per cent adrenalin spray, which he found effective in every instance in 400 attacks of asthma among 40 asthmatic. American physicians have not accepted this method as free of danger.

Stimulation to increased secretion. Attempts have been made to stimulate the adrenal glands to increased activity. Cohen and Rudolph did this with strychnine, which has been shown to stimulate the adrenals. They found that any good effect was overshadowed by the complicating hypertonicity from the pharmacologic action of strychnine.

Effect of adrenalin on positive skin reactions.—The question not infrequently arises whether one can perform reliable skin tests on a person who has recently had adrenalin. Formerly it was thought that adrenalin should be discontinued overnight or even for 24 hours prior to testing. However, Lamson, Tuft and Brodsky, and Swineford and Grove have shown that diminution in the intensity of skin reactions following a single dose of adrenalin disappears almost invariably within one hour. It commences early, within ten minutes.

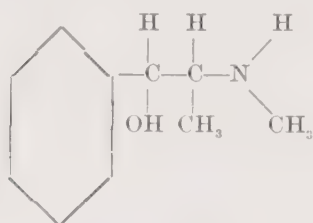
Tuft and Brodsky found that ephedrine, asthmolysin, pituitrin and aminophylline exerted a similar effect but decidedly less pronounced. Calcium gluconate, atropine and sodium iodide exerted no influence on skin reactions.

There is another situation in which the reliability of skin testing has been questioned. This is the individual with intractable asthma who must receive adrenalin injections every few hours over many days. These patients often fail to give satisfactory skin reactions. No study has yet been reported on the duration of inhibition of skin reactions by adrenalin in this type of case.

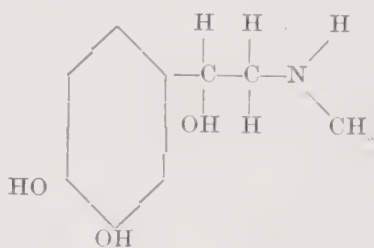
Ephedrine

The herb, Ma Huang, of which ephedrine is an alkaloidal active principle, has been used by Chinese physicians for some 5,000 years. It is said to be one of the drugs which was tasted by the Emperor Shen Nung. The herb was recommended as a circulatory stimulant, diaphoretic, antipyretic, and cough sedative. The active principle of *Ephedra vulgaris* (Ma Huang) was first isolated by Yamanashi in 1885, and Nagai obtained the alkaloid in pure form in 1887. He named it ephedrine. Amatsu and Kubota (1917) demonstrated its epinephrine-like activity. Soon thereafter it became widely used in Japan in the treatment of asthma. Chen and Schmidt commenced the study of the drug in this country in 1923. Since their introduction of the drug to the Western World with their very extensive pharmacologic investigations, it has become as well known and almost as important as adrenalin.

Chemically and pharmacologically ephedrine is very similar to epinephrine. The chemical similarity is obvious in the following formulae.



Ephedrine



Epinephrine

Ephedrine, like epinephrine, is sympathomimetic, exerting its activity through stimulation of the sympathetic nervous system. While the majority of investigators believe that, like epinephrine, it acts upon the myoneural junction, some believe that it acts upon the muscle itself. Like adrenalin, this drug in suitable doses raises blood pressure, increases cardiac activity, dilates the pupils, relieves bronchospasm, causes uterine contraction and either inhibits or, less frequently, stimulates the musculature of the gastrointestinal tract. Epinephrine increases heart rate, but resulting vagus stimulation may subsequently slow the heart. This latter phase is more pronounced with ephedrine. It is of some interest that, although the ancient Chinese herb was used in China through the centuries as a diaphoretic and antipyretic, the alkaloid, ephedrine, has little effect upon sweating and does not alter body temperature. It does slightly increase the basal metabolic rate and oxygen consumption. As with adrenalin, an increase in the formed elements of the blood and hyperglycemia follow its administration in suitable quantity.

Compared with epinephrine, ephedrine has both advantages and disadvantages. Its advantages are that it may be given by mouth and is not de-

stroyed by digestion; it may be employed as a preventive; it has more prolonged action; and produces less side reaction from overdosage. It is stable, not being decomposed by exposure to air, light, or heat. Its chief disadvantage lies in its lessened therapeutic activity compared with adrenalin. Also, some persons have become sensitized to ephedrine. However, in these cases synthetic ephedrine or ephedrine-like drugs may be used.

Clinical application.—Miller (1925) first reported benefit in the treatment of bronchial asthma with ephedrine. Soon thereafter Vallery-Radot and Blamoutier emphasized that, when given early, ephedrine will often abort attacks but that, an attack once having been established, it is less effective than epinephrine. They found it effective in 69 per cent of asthmatics when given prophylactically, in 43 per cent when given during the attack. Gaarde and Maytum (1926) first reported relief of hay fever following oral administration of ephedrine. It was first used locally in the nose and throat by Cook. Miller first reported its benefit in urticaria and Kesten first reported on a study of its use in chronic urticaria and angioneurotic edema. Stokes and McIntyre first reported its beneficial effect in the relief of drug allergy, following arsphenamine reactions. Saxl first reported benefit in senile emphysema.

Alexander and Kountz extended the study of ephedrine and epinephrine in obstructive emphysema such as accompanies bronchitis and asthma. They found that, whereas in normals the vital capacity increase averaged 350 cc. after 0.5 cc. of epinephrine, most patients with emphysema showed still greater increase. Patients with associated asthma did not do as well as those with associated bronchitis, due apparently to the difficulty of expelling thick tenacious mucoid sputum. Those patients with emphysema and bronchiectasis did not respond to epinephrine. The authors recommended ephedrine as a routine therapeutic agent of choice, chiefly because of its more prolonged action.

Like adrenalin, ephedrine may be used early in acute circulatory collapse but is not indicated in the late stages, where fluid replacement in the blood vessels, with saline or, better, transfusion, is the proper procedure.

Administration and dosage.—The drug may be given by mouth or percutaneously. It has some effect when given by rectum. Applied locally to the nasal mucosa in from 1 to 3 per cent it acts similarly to epinephrine. For such local application it is available in aqueous solution; in oil, either pure or mixed with aromatic ingredients; and in a water soluble jelly. Aqueous sprays are preferable to sprays in oil which may, on aspiration, cause serious pulmonary irritation, even pneumonia.

By mouth it is customarily given in capsules on account of the bitter taste. Usual dosages are 25 and 50 mg. This may be given three or four times daily or more often as indicated. Children usually tolerate the same dose although from 10 to 15 mg. has been recommended for children between six months and five years and 5 mg. under six months. Such doses may be given with 20 minims of glycerin and enough chloroform water to make one drachm. Relief is obtained in from 20 to 30 minutes when given by mouth; in 10 to 15 minutes when given intramuscularly or subcutaneously.

Ephedrine may be used for the same purposes as adrenalin. It is less effective but may be given by mouth and as a rule its action is more prolonged. In general it is better administered early in the development of an allergic attack than late, after symptoms have become more severe. In the latter case adrenalin is more effective. After a patient has been relieved

with adrenalin, relief may often be continued with ephedrine. Kampmeier reported relief of a young adult with migraine. Ephedrine in three-eighth grain doses aborted about 75 per cent of attacks if taken early enough.

Side effects.—The common subjective side effects are similar to those following epinephrine and include palpitation, trembling, weakness, feeling of warmth, chilly sensation, nausea, vomiting, insomnia, nervousness, drowsiness.



Fig. 297.—Proper instillation of nose drops. After drops are introduced the head should be lowered so that they may gravitate to the upper portion of the nasal fossa and the turbinates.

Many persons have no such reactions. Their occurrence appears to be a factor of the individual rather than of dosage. Less common symptoms include precordial pain, numbness and tingling of the extremities, constipation, diuresis, urinary retention, colitis, extrasystoles, tachycardia, albuminuria, hematuria, paroxysmal tachycardia, pulsus alternans. One case has been described in which it had an aphrodisiac action. I have seen a patient who always responded with priapism, another who always developed a urethral discharge. Like epinephrine it may exaggerate hyperthyroid predisposition.

These side effects may occur singly or in groups. With the exception of nervousness they are rare and usually not too inconveniencing. Nervousness and insomnia may be counteracted with one of the barbiturates such as phenobarbital, luminal, or amytal in 30 mg. ($\frac{1}{2}$ grain) or slightly larger doses.

Ephedrine appears to have no cumulative harmful effects and does not cause habituation. Hypertension is not a contraindication except in the presence of circulatory collapse.

Sensitization.—Very rarely one becomes sensitized to ephedrine. Bullen, Francis and Parker reported two cases of dermatitis medicamentosa. Kern and Schenck have described a similar case. A number of investigators have described dermatitis venenata from local contact, usually involving portions of the face, from application within the nose.

In these cases one of the synthetic ephedrines can usually be substituted.

Synthetic Ephedrine and Ephedrine-like Compounds

Ephedrine was first prepared synthetically by Fourneau in 1904. While natural or l-ephedrine is optically active, synthetic or dl-ephedrine is optically inactive. It is marketed under the trade name Ephetonin. Its pharmacologic action appears to be the same. The dose is likewise the same. D-ephedrine is less effective.

Ephetonin.—Kern and Schenck found ephetonin equally as efficacious as natural ephedrine in the palliative treatment of asthma, hay fever and vasomotor rhinitis. The synthetic drug, orally administered, in 25 mg. doses, had less tendency to raise the blood pressure. Unfavorable side effects were produced in about 9 per cent with ephetonin and in over 23 per cent with ephedrine.

Of 100 patients receiving both drugs at different periods, 16 obtained no relief from either drug; 32, equal relief from both drugs; 15 experienced more relief from ephedrine and 32 experienced more from ephetonin.

Compounds related to ephedrine.—A number of synthetic compounds differ from ephedrine or adrenalin only slightly in chemical structure. Many have been tried in allergy and some are available commercially. The first of these, phenylethanolamine, was synthesized by Kolshorn in 1904. It has satisfactory ephedrine-like action on the nasal mucosa but is useless when taken by mouth. Beta-phenylethylamine (Alles) also possesses this disadvantage. The synthetics which have found a place in clinical allergy are Neo-Synephrine, Benzedrine, and Propadrine.

Synephrin differs from epinephrine in that only one hydroxyl group is attached to the benzene ring instead of two. Its action is weaker than that of epinephrine.

Neo-Synephrine and Propadrine.—Neo-Synephrine and Propadrine are available in capsule form for internal administration. These and benzedrine are available in solution for local application in the nose.

In general it may be said that these exert a satisfactory action locally in the nasal mucosa but are usually not as effective as ephedrine when taken internally. Occasional cases do as well and they are therefore worthy of trial, especially with those who experience unpleasant side effects from ephedrine.

Black (1937) has compared the effectiveness of ephedrine and Propadrine (phenyl-propanol-amine). The outstanding advantage of the latter is the absence of nervousness and insomnia which makes it possible to use Propadrine at frequent regular intervals, even at night, and obviates the necessity of combining it with a sedative. Hay fever patients and asthmatics using aque-

ous and oily solutions in the nose reported results comparable to those with ephedrine. Propadrine capsules contain 24 mg. dosage. Severe asthmatics were often relieved with 48 mg. every 3 hours. This dose could be continued without ill effect. The duration of action is not longer than 3 hours. Children, six years old, tolerated 48 mg. without unpleasant effect. Customary dosage had no effect upon blood pressure. Rarely patients experienced nausea, sometimes with vomiting after several doses. Propadrine every 3 or 4 hours gave more relief to patients suffering with urticaria and angioneurotic edema than any other medication studied.

Benzedrine.—Benzylmethyl-carbinamine has recently attracted wide attention, not so much on account of its value in allergy as because of its unusual psychic stimulating activity. Benzedrine is a sympathomimetic drug which appears in addition to have an independent stimulating activity on the higher cerebral functions. It is more effective than ephedrine in narcolepsy. Although in larger dosage it increases blood pressure, 10 to 20 mg. by mouth produce euphoria, exhilaration, diminished fatigue, increased energy and capacity for work and increased verbosity. Slight overdosage may result in prolonged insomnia and nervousness. Metabolic rate and blood sugar levels are not affected by the above dose.

Waud has described the effects of toxic doses (10 grains). This is 50 times the usual therapeutic dose by mouth and approximately 1,000 times the usual therapeutic dose in the benzedrine inhaler. In the test benzedrine was inhaled. Toxic signs and symptoms included blurring of vision, dilatation of pupils, loss of smell, nasal dryness, pounding in the ears, dryness of the mouth and pharynx, sore throat, dyspnea on exertion, râles in chest, extrasystoles, paroxysmal tachycardia, bradycardia (on one occasion), loss of appetite, abdominal discomfort with distention and constipation, diuresis followed by urinary suppression and failure to realize when the bladder was full, blanching of the extremities, profuse perspiration, secondary mental depression, tremor of the hands and hypertension.

Boyd (1938) has found that even in dilutions of 0.05 and 0.01 per cent, benzedrine, ephedrine and neosynephrine exert a depressant action on ciliary movement.

Benzedrine inhaler.—A benzedrine inhaler may be used for application of the vapor in the nose. This is to be sniffed only at prescribed intervals, usually every two hours or longer, since constant sniffing may produce unpleasant side effects, especially extrasystoles or even paroxysmal tachycardia.

Scarano has described a secondary returgescence with atony and boggi-ness of the nasal mucosa when ephedrine is used locally over an extended period. He compared this type of response to benzedrine solution, benzedrine inhalant and ephedrine. On local application both solutions commence shrinking action within one minute. Although benzedrine was slightly slower both drugs produced maximum shrinkage within five minutes.

Secondary reactions, mentioned above, were studied in two phases; (1) one hour after initial application; and (2) after the drugs had been applied locally several times daily for a week or longer. One hour after initial application, 32 per cent showed secondary reactions from ephedrine, 20 per cent from benzedrine solution, and 8 per cent from benzedrine inhaler. After prolonged use 20 per cent showed reactions from ephedrine, 12 per cent from benzedrine solution, and 4 per cent following benzedrine inhaler.

Benzedrine inhalations in asthma.—Swineford (1938) finds that volatilized benzedrine may be inhaled through the mouth in asthma as it is through the nose in hay fever. The nasal inhaler is not satisfactory because the opening is too small and the menthol is irritating. A glass tube about the size and shape of an average test tube, open and annealed at each end, is constricted moderately in the center. Gauze is stuffed loosely into the distal end. One or 2 cc. of liquid benzedrine base is poured onto the gauze. The patient places the proximal end inside the lips, inhaling deeply. Inhalations through the tube should be made not oftener than once each minute, to allow time for the benzedrine to act and to prevent overdosage. As a rule 6 or 8 such inhalations are sufficient. This may be repeated as needed. The treatment may be combined with adrenalin injections.

Other preparations in use are Vonedrine, Nethamine, and Tuamine. These are vasoconstrictors with little or no central stimulation.

Various vasoconstrictor drugs have been combined with a sulfonamide and advocated as nose drops. There is some question as to the possibility of sensitizing the patient by prolonged use of a sulfonamide on the mucosa of the nose. Tyrothricin is used in combination with Propadrine. There is no evidence that it causes sensitization.

Ergotamine

Ergot, a parasitic fungus of rye and occasionally of other plants, has been extensively studied in the past as to its toxicologic and pharmacologic activities. Stoll isolated an alkaloid which he named ergotamine. This alkaloid resembles epinephrine in some of its effects and, like it, acts on the myoneural junctions of the sympathetic nerves. While epinephrine stimulates both motor and inhibitory fibers, according to Edmund and Gunn ergotamine has no effect on inhibitory junctions and, although stimulating motor junctions in small doses, paralyzes them in larger quantities. Ergotamine acts on the circulation as does adrenalin and apparently by the same mechanism, with rise in blood pressure due to contraction in the vessel walls and cardiac acceleration. However, Rothlin has recently presented evidence that ergotamine is in a sense antagonistic to epinephrine. Adrenalin effect is obtained by stimulation of the sympathetic excitatory junctions. Ergotamine appears to stimulate only the sympathetic inhibitory junctions. Adrenalin stimulates both but the excitatory activity preponderates. If this is the case, ergotamine and epinephrine stand in the same relationship with regard to the sympathetic nerves as is occupied by atropine and pylocarpine for the parasympathetics. The pharmacology of ergotamine needs further study.

There is clinical evidence that ergotamine relaxes cerebral vascular spasm. At any rate it has been shown to be almost specific for relief of the pain of migraine.

Ergotamine tartrate.—This drug, used in migraine, may be given by mouth (1 mg. tablet), hypodermically or intramuscularly or even intravenously (0.25 mg. to 0.5 mg.). It is more effective when taken early in the attack. The preferable route is intramuscular. An ordinary hypodermic needle is used, introduced vertically through the skin into the deltoid or other muscle.

If the drug is effective orally in dosage of 1 or 2 mg. this method should be continued. If it is not effective, intramuscular or deep subcutaneous injections of 0.25 mg. or 0.5 mg. should be attempted. Usually this is more reliable.

The proper dose having been determined, there is rarely need for subsequent increase. If treatment is not started until the attack is well advanced, larger doses are often needed. About 10 per cent experience nausea and vomiting following ergotamine tartrate, after which the headache rapidly disappears. Headache may disappear without nausea or vomiting. Relief is usually obtained in from thirty minutes to one or two hours. It is usually permanent for the individual attack. The following day, patients may complain of muscle pain or soreness, stiffness of the joints or weakness with numbness and tingling of the extremities, symptoms which if necessary may be relieved with atropine sulphate (1/100th grain) by mouth or calcium gluconate orally or intravenously.

Lennox and Von Storch found that the drug gave abrupt and complete relief from the attack in 107 of 120 patients with migraine. Nineteen used it for more than a year without deleterious results. In some patients a tendency for the headaches to recur at more frequent intervals or the development of unpleasant side symptoms limited its use.

Contraindications are organic vascular disease, hyperthyroidism, icterus, septic infection and pregnancy. A few cases of ergotism with gangrene of the feet have been reported. In the absence of contraindications the drug may be used for long periods, but it is to be borne in mind that it carries with it some element of danger, that it is merely a symptomatic remedy, and that its use does not justify failure to search for and remove the specific causes of the migraine.

Ergotism, gangrene. The possibility of this complication appears to be remote in uncomplicated cases. O'Sullivan (1936) reported the successful termination of 1,000 attacks of migraine with ergotamine tartrate, without complications. The literature on gangrene from this drug has recently been reviewed by Yater and Cahill (1936) and by Gould, Price and Ginsberg (1936). In most cases total dosage was much higher than is used in migraine, varying from 6.5 to 117 mg. However, in certain conditions, notably icterus, hyperthyroidism, arteriosclerosis, coronary disease and chronic sepsis, very small doses have produced gangrene and even death. The drug should not be used in these conditions. The smallest amounts that have produced gangrene are 1 mg. given subcutaneously in a 4-day period and 26 mg. given by mouth over 7 days. In the first case the drug was given for relief of pruritus in a patient with jaundice and vascular disease. The second case was one of puerperal sepsis.

Obviously ergotamine should not be used continuously in migraine. When used over a prolonged period careful watch should be kept for symptoms of early ergotism: painful extremities, pallor followed by cyanosis. The pathologic response appears to be a general spastic narrowing of the arterioles, with slowing of the blood stream and thrombosis. The blood flow in the femoral artery has been found diminished to 50 per cent of normal or less in dogs receiving 0.5 to 1 mg. ergotamine tartrate intravenously. Similar injections in the cat have been followed by constriction of the arteries of the dura and skin.

Most persons with threatened gangrene from ergotamine progress in spite of all treatment. Perlow and Bloch (1937) report cure of impending gangrene from 1 mg. by mouth and 2.5 mg. subcutaneously (for icteric pruritus) by administration of papaverine hydrochloride. One-half gram was given intravenously twice on the first day, by mouth twice on the second day, and

once the third. Pavex treatment with the suction and pressure boot was also given intermittently for three days. However they attribute relief chiefly to the papaverine acting as a peripheral circulatory antispasmodic. Dihydro-ergotamine (D.H.E.-45) is a newer preparation which appears to give as good results as ergotamine and causes less nausea, less uterine cramps and seldom causes symptoms of ergotism.

The Xanthine Compounds

Caffeine.—There is no adequate pharmacologic explanation for the occasional remarkable benefit from caffeine or black coffee in asthma and migraine. Caffeine stimulates the central nervous system, especially the psychic functions, and makes one less conscious of fatigue. It increases capacity for physical work. It accelerates the pulse, due to direct stimulation of cardiac muscle, and widens the terminal vessels, again from direct action. It dilates the coronary vessels, increases the respiratory rate, and causes diuresis. The only two effects that might appear logically to explain benefit are the fact that a bronchodilator action has been described and that vagus stimulation is less effective in slowing the heart in the presence of caffeine. However, the lessened vagus or parasympathetic effect is not due to partial paralysis of the nerve ends but to increased irritability of the heart muscle.

Nevertheless, an occasional asthmatic finds as great relief from hot coffee as from adrenalin. I have seen two asthmatics who did not tolerate adrenalin at all because of hyperergic response, with extreme nervousness, tremor and tachycardia but who always obtained relief with coffee. I have seen a third with very severe asthma which did not respond to adrenalin although there were no symptoms of adrenalin intolerance, but who was promptly relieved after an intramuscular injection of seven and one-half grains of caffeine sodium benzoate.

Aminophylline. Theophylline. Theocine.—This, another of the xanthine diuretics, appears to differ from caffeine chiefly in its greater diuretic action. Herlitz reports satisfactory results in the treatment of asthma in children with caffeine derivatives. He used a tablet to be taken internally containing 0.015 grams of theobromine calcium salicylate and 0.035 grams of theophylline. He prescribed theobromine calcium salicylate 15 mg. ($\frac{1}{4}$ grain) with theophylline 35 mg. ($\frac{1}{2}$ grain) orally. Tuft and Brodsky have found that aminophylline, like adrenalin, tends to diminish the intensity of positive skin reactions, and Tuft recommends it for the relief of acute asthmatic paroxysms which have not responded to other therapy.

Herrmann and Aynesworth who report relief in 16 cases of adrenalin-fast status asthmaticus state that although they have found reports of respiratory improvement after aminophylline, there has been no report of pulmonary circulatory augmenting effect, of smooth muscle relaxation, or of bronchial clearing effect. The few reports of respiratory effect have intimated central nervous system action. They quote Boek as demonstrating dilatation of the blood vessels of the isolated dog's lungs.

Aminophylline tablets, $1\frac{1}{2}$ to 3 grains, by mouth, are effective in relieving mild asthmatic attacks. Intravenous injection is much more effective, and frequently brings dramatic relief when epinephrine has failed. Seven and one-half grains are usually well tolerated by the adult, and smaller doses may not be effective. Injections should be given very slowly to avoid unpleasant symp-

toms such as flushing, weakness, palpitation, and even collapse. A few deaths have been reported following intravenous use, but this is rare and should not prevent the use of this valuable drug. If injections are given slowly enough, symptoms of any kind rarely appear. It is possible to use 7.5 grains in 2 c.c. with a 26-gauge needle if the solution is introduced drop by drop. This is more pleasant for the patient and does less trauma to the vein. Extravasation into the tissues is very painful, as is intramuscular injection.

Aminophyllin with or without ephedrine or Propadrine seems to be helpful in the treatment of urticaria and hay fever. There are a number of tablets available on the market with such combinations under the trade names of Tedral, Padrophyll, Amodrine, Luasmin, Amsec, Adnephryn, etc.

Enteric coated tablets of aminophylline or a combination as just mentioned can be given at bedtime to prevent the occurrence of asthma in the early morning hours. Many patients will be able to sleep all night with this form of protection.

Aminophylline suppositories are almost as effective as intravenous injection, and may be used instead of the injection making the control of the severe attack much easier (Dees).

Baldwin* finds aminophylline of value in controlling the constitutional reaction. A man with severe cyanosis and dyspnea after an injection of castor bean extract was not relieved following tourniquet application and adrenalin 0.5 cc. every 5 minutes for four doses. Four grains of theophylline with ethylenediamine intravenously was followed by improvement within one minute with rapid recovery thereafter.

A mixture of aminophylline 0.12 grams (2 grains), ephedrine 25 milligrams ($\frac{3}{8}$ grain) and a barbiturate such as phenobarbital 30 milligrams ($\frac{1}{2}$ grain) given every three or four hours is often beneficial in acute allergic episodes, especially in hay fever and asthma. When theophylline is combined with propadrin, the hypnotic need not be included.

II. DRUGS WHICH ACT PRIMARILY THROUGH INHIBITION OF PARASYMPATHETIC ACTIVITY

These include atropine, belladonna, stramonium and hyoscyamus. These alkaloids are derived from members of the Solanaceae, the tobacco-potato family, being obtained respectively from deadly nightshade (*Atropa belladonna*), jimson weed or thorn apple (*Datura stramonium*), and henbane (*Hyoscyamus niger*). They all exert rather similar effects.

Atropine

This drug affects a number of organs, especially those containing smooth muscle or secretory glands, through depressant or paralyzing action on the terminations of the parasympathetic fibers. It also stimulates the central nervous system. Atropine decreases most of the secretions, not through action upon the secretory cells but through paralysis of the parasympathetics with resultant failure of nervous impulses to reach the glands. This applies not only to the glands of the mouth, throat, nose and respiratory passages, but also to the digestive and sweat glands. The mammary gland and kidney, largely independent of secretory nerves, are not affected nor is the secretion of lymph.

*Baldwin, Horace S., New York, N. Y. In the International Correspondence Club of Allergy.

Organs containing nonstriated muscle, except for the arteriolar walls, are affected by atropine. Bronchial muscle does not contract under vagus stimulation, after atropine has paralyzed the myoneural terminations. On the other hand, atropine does not actively dilate the bronchi (muscular relaxation) and this undoubtedly accounts for the much greater therapeutic efficacy of adrenalin in asthma.

Atropine has a sedative effect on the musculature of the stomach and intestines. In small doses it does not affect normal peristalsis but does prevent hyperperistalsis and tetanic contraction. It affects the spleen, uterus, gall bladder, urinary bladder and ureters in a similar manner. Since it paralyzes the inhibitory terminations of the vagus in the heart, stimulation of the latter causes no change in pulse rate. Edmunds and Gunn state "the organs thus affected receive their innervation from the autonomic system, some of them from the parasympathetic division, some others from the sympathetic; atropine cannot be said to affect either of these divisions exclusively, but its action on the myoneural junctions of the parasympathetic division is more prominent than that on the sympathetic."

The dose of the pure alkaloid is $\frac{1}{2}$ mg. or $\frac{1}{120}$ th grain. It is less frequently employed in the allergic diseases than the less highly purified preparations, chiefly because the latter are absorbed more slowly and exert their effect over a longer period.

Evidence has been brought out by Myerson that although atropine alone is less effective than epinephrine, a combination of epinephrine and atropine should be more effective than epinephrine alone. The two appear to work synergistically, atropine counteracting parasympathetic effect and thereby facilitating the adrenergic action of epinephrine. This applies equally to ephedrine, benzedrine and the other synthetic compounds. It should therefore be a logical procedure to prescribe one of these together with atropine, tincture of belladonna, or belladonna and hyoscyamus. Unfortunately, however, atropine renders the bronchial secretions more viscid and adds to the patient's difficulty so it is seldom used.

Belladonna

Belladonna may be prescribed as the leaves in dose of 60 mg. or 1 grain; the extract in dose of 15 mg. or $\frac{1}{4}$ grain or more frequently as the tincture, 0.6 cc. to 1 cc. (10 to 15 minims). The extract or the tincture may be used in colitis, including allergic colitis, to lessen abdominal pain associated with hyperperistalsis. The impure preparation exerts a stronger local effect than the pure alkaloid because of its slow and imperfect absorption as contrasted with the latter which is rapidly absorbed in the duodenum. In some cases atropine or belladonna has as beneficial effect in allergic coryza as it does in acute infectious coryza. It is less effective in asthma, but may be tried when other measures, especially adrenalin or ephedrine, have not given adequate relief. It may be used with them. Atropine has been applied to the bronchial mucosa locally as a spray.

Hyoscyamus

This may be used in the same conditions and for the same purposes as belladonna. The dose of the tincture is 1 to 2 cc. (15 to 30 minims); of the fluid extract 0.2 cc. (3 minims); of the extract 50 mg. or $\frac{5}{16}$ grain.

Hyoscyamus is said to exert a greater sedative action on the gastrointestinal tract than belladonna and is often used in preference in hyperperistalsis and colitis. The writer recommends especially equal parts of tincture of belladonna and tincture of *hyoscyamus*, in a dose of 15 or 20 minims before meals and at bedtime, or every four hours.

Stramonium

This may be used in the same way, the dose of the tincture being 0.75 cc. or 12 minims; of the extract 20 mg. or $\frac{1}{3}$ grain. Its chief use in allergy is in asthma for which the dried pulverized stramonium leaves are incorporated in asthma powders which are to be burned, the smoke being inhaled. To insure combustion the dried leaf is mixed with an equal quantity of saltpeter (potassium nitrate).

Asthma powders.—Asthma powders have been of great aid to those asthmatics who have been unable to avail themselves of allergic therapy. The basic ingredients are stramonium leaves and potassium nitrate. Although the latter is incorporated to assure combustion following ignition, beneficial action is also attributed to it. Edmunds and Gunn state that combustion of saltpeter results in pyridine and nitrite which relax bronchial musculature. Potassium nitrate has been used in cigars and cigarettes for the same purpose. Some asthma powders contain only these ingredients while others contain one or more of the following: lobelia leaves, mullein, swamp cabbage, cubeb, camomile, saw palmetto, eucalyptus, thyme, aniseed, fennel seed. Practically all of the asthma powders and cigarettes are proprietary preparations.

Sensitization to asthma powders.—Swineford has described the case of an asthmatic allergic to the asthma powder which she customarily used. The patient had used about three cans a month for six years, obtaining excellent relief for the first five years. During the last year relief was very evanescent, lasting only for a few minutes, after which the asthma increased. On one occasion, while getting out of her car she spilled some of the powder on her coat and promptly had a violent attack of asthma. Swineford then tested her with the ingredients of the powder, stramonium leaves, swamp cabbage, lobelia and potassium nitrate, obtaining positive scratch, endermal and passive transfer reactions to the first three. He concludes that patients should be tested with extracts of asthma powders or cigarettes before they are permitted to use them and that those who are using them should be tested periodically for sensitization.

III. THE OPIUM DERIVATIVES—NARCOTICS

Contraindications.—Members of the opium series act chiefly by depression of the nervous system, with relief of pain and slowing of the respiration. They induce constipation by causing relaxation of the stomach wall and increased tone of the intestines, apparently through local action. Morphine and the opium derivatives differ from alcohol in their action on the central nervous system in that it is predominantly upon the respiration and pain sensation rather than on the higher cerebral functions. None of these chief effects are especially desirable in the treatment of the allergic diseases, and on the whole they are to be avoided. Other pharmacologic activities of the opium group have no bearing on allergy. In only two allergic states, asthma and migraine, do we find discussion of indications for morphine. It should

not be used in migraine, first because of the possibility of addiction and second because of the greater therapeutic efficiency of ergotamine tartrate in most instances. With regard to asthma, the statement is sometimes made that morphine should not be used except as a last resort. The writer feels that this is precisely the time when morphine should not be used. Numerous allergists have remarked on the frequency of a record of recent morphine administration to persons who die during status asthmaticus. The patient who is *in extremis* with severe intractable status asthmaticus should not receive morphine. He is already fighting for his breath with every ounce of energy that he has and the slowing of the respiration from morphine may be just enough to determine death from asphyxia. If morphine is to be used at all in asthma it should be in the less critical cases, where its occasional beneficial effects probably result from relaxation and the dulling of that sense of apprehension which undoubtedly exaggerates symptoms in some cases.

The importance of the apprehension factor is well illustrated in the two following cases.

A young woman with severe intractable asthma over a period of many months always improved when her sister informed her that the doctor was coming. While she had constant asthma, there were periods of severe exacerbation, during which the sister would call asking that one of us come quickly. On arrival we rarely found her condition as serious as her sister had led us to believe. On one occasion the sister remarked that it was curious that whenever she informed the invalid that the doctor was on his way she promptly improved. Her sister was disappointed that we could never see her at her worst.

The second case* was that of a woman who had been in the hospital with severe asthma for some time but had been relieved and returned home. A few days after her return home she was free from asthma but was uncertain concerning the contents of two bottles of asthma medicine which did not look or smell alike but were supposed to be identical. The doctor tasted them both, agreed that they were different and took them back to the druggist who also tasted them, reaching the same conclusion. Upon his return to the office he received an emergency call from the patient's husband telling him that a serious error had been made, that during her sojourn in the hospital hair tonic had been placed in one of the bottles. The patient and her husband were extremely anxious concerning possible poisoning of the doctor, and their apprehension was doubled when they discovered that the pharmacist had also tasted the hair tonic. The patient promptly went into severe asthma which was not relieved until investigation of the hair tonic had been made and she was assured that it contained no poison.

Thieme and Sheldon (1938) who report necropsies on 17 asthmatics, 7 of whom died in status asthmaticus, conclude that morphine and atropine should never be used in the management of status asthmaticus. Morphine depresses the respiratory center and the cough reflex, permitting accumulation of bronchial secretion. Atropine tends to thicken the bronchial secretion, increasing the difficulty of raising mucous plugs. They believe that if the drugs are used at all in the management of the milder asthmatic paroxysms they should be given with extreme care and in small dosage.

There have undoubtedly been instances in which moderately severe asthma has been relieved in great measure by morphine, but the probability is that most of these would have been more adequately relieved with proper adrenalin and other therapy.

Codeine

Because of its less depressing action codeine is to be preferred to morphine when its use seems imperative. The following procedure which was suggested to the writer several years ago by Davison† is often promptly effective in cases not sufficiently relieved with epinephrine.

*Evermann, Charles H., St. Louis. Personal communication.

†Davison, Hal M., Atlanta. Personal communication.

One grain (60 mg.) of codeine phosphate and 1/60th grain (1 mg.) of apomorphine are dissolved in 1 cc. of 1:1,000 adrenalin. The entire amount is placed in a hypodermic syringe. The first injection is one-third of the amount. This is repeated twice at twenty-minute intervals if necessary. More than a total of three injections is rarely required for more or less prolonged relief. Often the first injection is sufficient.

Apomorphine has practically no depressant action on the central nervous system but is rather a stimulant. The customary dose as an emetic is 5 to 10 mg. (1/12 to 1/6th grain). The dose described above is not sufficient to stimulate the vomiting center but is enough to cause slightly increased secretion in the bronchial tree.

What has been said of morphine applies equally to other opium derivatives: codeine, papaverine, narcotine, and artificial compounds such as diionine (ethylmorphine), dilaudid and heroin (diacetylmorphine). It also applies to pantopon, a preparation containing all of the alkaloids of opium in the same proportion in which they exist in opium itself. All allergic episodes, no matter how acute at onset, carry with them the possibility of being long continued. This carries the potentiality of drug habituation. Whenever possible, opiates should be avoided.

Demerol

Demerol is ethyl 1-methyl-4-phenylpiperidine-4-carboxylate. It is a synthetic compound which chemically and pharmacologically resembles both morphine and atropine. It may be used for the relief of severe pain and to relax smooth muscle spasm. It has been recommended for the relief of status which has been found refractory to epinephrine and aminophylline. It may be administered by mouth or subcutaneously in dose of 50 to 100 mg. It is said not to depress the respiratory center and therefore to be much safer than the opiates. There is some argument as to the development of addiction to the drug. Huber* has recently reported a death in status asthmaticus following the administration of Demerol.

Cocaine

This alkaloid is derived from the leaves of the coca bush (*Erythroxylum coca*), a shrub of the Peruvian Andes which has been cultivated from early times. The South American Indian chewed the leaves as a stimulant. It is not related to cocoa (chocolate) the fruit of a tree *Theobroma cacao*.

Cocaine is used primarily as a local anesthetic. It is a general protoplasmic poison. Allergy to cocaine is not extremely common but, when it does exist, is usually intense and may play a part in many of the sudden deaths following the injection of cocaine as a local anesthetic. The majority of these fatalities have occurred in nose and throat work and have usually followed the use of strong solutions, 10 or even 20 per cent.

Local application.—The use of a mixture of cocaine and adrenalin or ephedrine in aqueous solution as a nasal spray may at times be considered in hay fever. In those cases which respond adequately to one of the adrenergic drugs, cocaine should not be used. In the majority of cases the addition of cocaine gives greater relief. According to Edmunds and Gunn the action of cocaine is quantitatively modified to an important degree by the simultaneous use of epinephrine. Local vasoconstriction from adrenalin relieves congestion

*Huber, H. L.: Personal communication.

and lessens hemorrhage, at the same time delaying absorption of the cocaine. This allows a longer time for its excretion or destruction in the body and thereby diminishes its toxicity. In other words the simultaneous use of both diminishes the probability of systemic effect. Furthermore, a local nasal spray containing cocaine may be more dilute than that usually used in surgery. A mixture containing equal parts of 2 per cent cocaine hydrochloride and 3 per cent aqueous ephedrine, giving a final concentration of 1 per cent cocaine and 1.5 per cent ephedrine, gives adequate relief.

Such a mixture should not be used without preliminary testing for possible sensitization with a very dilute solution; and should not be used in perennial vasomotor rhinitis because of the possibility of habituation. The author has not found this a problem to be considered in seasonal pollinosis.

Cocaine has been shown to be a constituent of certain asthma nostrums, especially those used as sprays.

Other Local Anesthetics

Butyn and Nupercaine have been reported as causing much conjunctivitis and dermatitis from their use in the eye and on the skin. They may relieve the pain or discomfort for which they were prescribed and still produce a marked reaction. These same drugs used hypodermically seldom cause reaction. Sensitization is usually due to contact with epithelial surfaces. Butyn has been used in thousands of injections together with concentrated pollen extracts and no sensitization has ever been seen from this usage.

IV. ENDOCRINE PREPARATIONS

Bray has written a comprehensive summary of the literature on the endocrine factor in allergy. The part played by adolescence, the menopause, and pregnancy in appearing to initiate or terminate allergic episodes is well recognized since, in females, it occurs frequently enough to be noted. Some women have asthma or other allergic symptoms only during pregnancy, while others are relieved only during pregnancy. Boys are more likely to have symptoms prior to adolescence, with relief thereafter; while girls more often experience the reverse. However, all of these can be considered but tendencies, no clear-cut rule being followed in most cases. For example, in most women pregnancy has no effect. When it does it has been sufficiently interesting to justify a case report.

A similar situation exists with regard to the various glands of internal secretion. Somewhat reduced metabolic rates are observed more often in allergies than increased rates although both are seen. Bray points out that the reports are of isolated cases and for each case responding to endocrine therapy, there are numerous others in whom no direct improvement follows. He found no evidence in his study of allergic children that endocrine therapy, aside from epinephrine, was beneficial. He further calls attention to the obvious fact that allergic patients do not fall into any picture simulating increased or decreased function of any of the glands so far studied. Witts found in a study of 500 asthmatics, 350 of whom were over age fifteen: 0.6 per cent with myxedema; 0.2 per cent with hyperthyroidism; 0.4 per cent with Fröhlich's syndrome; and 0.2 per cent with diabetes. Hill found only 7 asthmatics among 422 patients with definite endocrine dyscrasias including cretinism, myxedema, hyperthyroidism, Addison's disease, virilism, hirsutism, eunuchoidism, cryptorchidism and castrates. The seven cases were found in eunuchoid and hypothyroid states. There were 166 patients in these latter groups.

Endocrine disturbances may occur among allergies as well as nonallergies. When they do, appropriate endocrine therapy should be administered entirely independently of the allergic state. There does appear to be some interrelationship between the two states occurring in a single individual to the extent that allergic therapy is usually more successful if the endocrine dyscrasia is properly controlled. Thus, a woman in our experience with atopic dermatitis and hypothyroidism was not adequately relieved until she had been placed on a diet and been given thyroid therapy. Thereafter a break in the diet or discontinuance of thyroid extract would result in return of dermatitis. Both factors required control. The allergy was not controlled until the endocrine state was adjusted. Conversely it was pointed out in the discussion of insulin allergy, that a case of diabetes was not controlled with insulin until allergic insulin reactions had been controlled.

In those cases in whom there is an exacerbation of symptoms (migraine, asthma, urticaria) periodically, either before, during or after the catamenia, appropriate opotherapy is often indicated, and sometimes contributes to relief when allergic therapy alone has failed.

Insulin

The infrequent coincidence of asthma and diabetes has been noted by several investigators. Swern observed only six diabetics among 4,000 allergic patients. He observed that when diabetes occurred in a person previously asthmatic positive skin reactions became less intense, and the asthma improved. König found three asthmatics among 1,240 diabetics. Thus we see that rarity of simultaneous occurrence is seen both ways. König suggests as an explanation, an antagonism between insulin and adrenalin.

Wegierko treated 40 asthmatics with insulin, giving 40 unit doses to fasting patients, with treatment every four or five days in mild cases, once or twice daily in very severe cases. He found that insulin shock relieved the asthma. Following relief, sugar was given. He does not recommend this procedure in patients with cardiovascular disease or tuberculosis, or in the aged. Theoretically one might assume that insulin shock calls upon the adrenals for increased secretion. It would seem easier to administer epinephrine hypodermically. Insulin treatment of asthma has not come into general use.

Theelin

Goldberg has reported relief from urticaria and angioneurotic edema due to sunlight and effort, occurring during the menopause, with theelin injections.

Pituitary Extract

Following some experimental work on the posterior lobe, it was suggested that extract of this lobe, acting as a vasoconstrictor, might act as an antagonist to histamine and prolong the effect of epinephrine. A combination of pituitary extract and epinephrine was placed on the market under the trade name of Asthmolysin. Results from its use were quite unsatisfactory. This combination has no advantage over the use of epinephrine alone.

Spleen Extract

Some years ago reports in the European literature of relief from asthma following irradiation of the spleen and the region of the hilus glands of the lungs, attracted some interest but gained no great following in this country.

That some investigators are still working on this subject is indicated by the observations of Hutter. Mayr and Monerops had studied the relationship between the spleen and eosinophilia. Impairment of splenic function was accompanied by eosinophilia, while increased splenic activity resulted in a diminution of blood eosinophiles. The injection of spleen extract, free from protein, diminished the percentage of eosinophiles in allergic dermatoses and promoted recovery.

Many efforts were made to show the efficacy of splenic extracts but all failed. It is now generally agreed that this substance is of no value in the treatment of allergic conditions.

Cortical Hormone

Immunologic features.—Steinfeld et al. have reviewed the literature on a possible relationship between vitamin metabolism and the adrenals. The adrenal gland is a rich source of vitamin C. The adrenal cortex undergoes hypertrophy in avitaminosis B and C, while it becomes atrophic in avitaminosis A. Ascorbic acid has been found to disappear from the adrenals of guinea pigs on scorbutic diet and to reappear after adequate amounts of orange juice have been added to the diet. Recent critical work by Grollman and Firor, however, would indicate that purified cortical extract has no protective effect on animals suffering from scurvy or vitamin B-1 deprivation. Likewise ascorbic acid will not counteract adrenal insufficiency in rats. Rockwood and Hartman have suggested the possibility that the cortical hormone may condition the amount of vitamin necessary or aid in its utilization. Cohen and Woodruff have found that vitamin C deprivation in guinea pigs does not predispose to sensitization or to anaphylactic shock.

Insufficiency or absence of cortical hormone appears to result in increased susceptibility to infection and toxin activity. This has been observed in adrenalectomized rats. Hartman and Scott have found that in such rats, adrenal cortex extract exerted a protective effect against the poisoning produced by injection of dead staphylococci or dead typhoid bacilli. Steinfeld and his collaborators found that adrenalectomized rats were incapable of withstanding large doses of dead typhoid bacillus and that they succumbed during attempts at immunization with graded doses of the vaccine. Marmorston and Perla found that bilateral adrenalectomy lowered the resistance of rats to infection with *Bartonella muris*. Dietrich has described edema of the adrenal cortex in protracted infection. Aschoff found degenerative changes especially in diphtheria, scarlet fever and septic infections, especially those due to streptococcus. Robbins has reported signs of advanced adrenal insufficiency accompanying a streptococcus throat infection, with prompt improvement after use of adrenal cortex extract.

Selye, in discussing the "alarm reaction," speaks of the changes in the adrenal cortex resulting from various conditions hurtful to the animal. These changes are protective in character at first but, after repeated "alarms" may become irreversible and may be responsible for a resulting cortical insufficiency.

Anaphylactic features.—Kepinow and Flashman have shown that anaphylactic shock may be produced with smaller doses in adrenalectomized animals than in normals, irrespective of whether the adrenals were removed before or after sensitization had been established. Perla and Marmorston found that the resistance of adrenalectomized animals to histamine shock was increased following cortin administration. Wolfrian and Zwemer have combined

TABLE LXXIII. VITAMIN INFORMATION FOR USE IN DIET PRESCRIPTIONS

VITAMIN	VITAMIN A	THIAMIN (B ₁)	RIBOFLAVIN (B ₂)	NICOTINIC ACID (P-P)	ASCORBIC ACID (CEVITAMIC ACID, VITAMIN C)	VITAMIN D
General Description	Fat-soluble. Plants synthesize to provitamin stage (carotene). Completion of synthesis in animal liver.	Water-soluble. White crystal. Stable in acid media.	Water-soluble yellowish pigment with green fluorescence, recognized years ago in milk and formerly termed lactoflavin. Probably exists in every living cell.	Water-soluble. Recent evidence indicates that this is the pellagra-preventive vitamin or provitamin. Present in all cells.	Water-soluble. Easily destroyed by oxidation. More abundant in growing tissues (sprouting seeds and parenchymatous organs). Is synthesized in all plants and animals except man, anthropoid apes and guinea pigs.	Fat-soluble. There are 10 varieties, 2 of which are important. The vegetable vitamin is derived from ergosterol, the animal vitamin from cholesterol.
Results of Deficiency	Chiefly in ectodermal tissues. Atrophy and hyperkeratosis of skin and mucous membranes. Xerophthalmia. Keratomalacia. Night blindness.	Beriberi. Peripheric neuritis. Anorexia. Retarded growth. Impaired intestinal motility (constipation). Edema. Tachycardia on exertion.	(Studied in rats only) 1. Stunted growth 2. Lowered body tone 3. Premature aging 4. Loss of hair 5. Eczema 6. Conjunctivitis, keratitis and cataract.	1. Pellagra, in man. This disease is sometimes relieved with nicotinic acid alone, sometimes with nicotinic acid plus other vitamins especially riboflavin and thiamin. 2. Black tongue, in dogs.	Scurvy. Hemorrhage (growth changes (bones, cartilage and teeth)	Rickets. Osteomalacia. Retarded growth
Function	In eye, combines with protein to form visual purple.	Promotes proper metabolism of carbohydrate by destruction of pyruvic acid.	An enzyme or catalyst controlling transport of oxygen into the cell. Function is therefore that of utilization of oxygen (oxidation).	Not clearly understood. Essential to the integrity of cells. Necessary for normal functioning of gastrointestinal tract, skin, central nervous system and probably, other systems	Reduction or utilization of hydrogen. Controls metabolism in connective tissues; the deposition of gelatinous substance between cells (capillary and connective tissue) and the extracellular tissue in bones, cartilage, teeth.	Normal deposition of calcium and phosphorus salts at ossification centers. Control of calcium and phosphorus metabolism.

Symptoms	Enough for several weeks, chiefly in liver. Also in lung and kidney.	Poor, because water-soluble and excreted in urine. Enough for only 10-25 days. Chiefly in liver, kidneys and heart.	As in thiamin. Some present in all cells.	Undetermined. Possibly like thiamin.	Very poor. Absence in diet for 1-2 weeks results in deficiency.	Probably good. Deficiency becomes a problem only in growing children and pregnant women.
Causes of Deficiency	<p>1. Inadequate diet</p> <p>2. Digestive disturbances</p> <p>a. Chronic diarrhea</p> <p>b. Bile tract disease</p> <p>c. Pancreatic disease</p> <p>d. Low fat intake</p>	<p>1. Modern methods of food preparation.</p> <p>a. Destruction in cooking.</p> <p>b. Leached out in boiling.</p> <p>c. Discarding of accompanying liquids of canned foods.</p> <p>d. Inactivation by baking soda.</p> <p>2. Failure to use germ and bran layers of seeds</p>	No specific human diseases have been attributed to riboflavin deficiency but the situation may well parallel that of thiamin deficiency.	Chiefly, poorly balanced diet.	<p>1. Inadequate diet.</p> <p>2. Destruction by modern methods of food processing (oxidation). The presence of alkali, use of copper cooking utensils, pickling, curing, and fermentation destroy it. It is absorbed from warmed over foods.</p> <p>It is more stable in acid foods, such as citrus fruits.</p> <p>Mother's milk contains four times as much as cow's milk.</p>	<p>1. Absence of sunlight in winter months (failure to manufacture animal vitamin D in body).</p> <p>2. Deficiency of milk in diet (symptoms result more from calcium deficiency than vitamin deficiency).</p> <p>3. Insufficient vitamin in diet (diet of weaned infants must be vitamin reinforced).</p>
Tests for Deficiency	<p>Test for night blindness. Biophotometer and adaptometer available for clinical use. Direct test in blood (Dann-Evelyn modification of Carr-Pierce reaction).</p>	Quantitative determination in urine or blood. Rather complicated for clinical use.)	No simple clinical test available.	No simple clinical test available.	<p>Quantitative tests in blood and urine.</p> <p>Indirect (capillary resistance) clinical test available. Reliable if negative. Endermal dye test (indophenol) not reliable.</p>	Indirect clinical tests include blood calcium, blood phosphorus, and occult blood in stool.

TABLE LXXIII—CONT'D

VITAMIN	VITAMIN A	THIAMIN (B ₁)	RIBOFLAVIN (B ₂)	NICOTINIC ACID (P-P)	ASCORBIC ACID (VITAMIN C)	VITAMIN D
Normal daily Requirements	3-5 mg. carotene or 1,500-2,000 international units. (1 U. = 0.0006 mg. standard beta-carotene). 1 quart milk + 1 egg + butter + 1 tsp. cod liver oil + green leafy vegetables = 5,000 to 8,000 I.U. = enough for growing child.	1-2 mg. in growing child and adults. (More in nursing mother.)	500 International Units or 2-3 mg.	Undetermined.	40 to 100 mg.	Children and adults 300-500 units. Premature infants and nursing mothers, 800 units. Minimal requirements = 0.002 mg. calciferol.
Therapeutic Dose	15,000 to 60,000 U.S.P. Units	4-50 or more mg. daily	Not known.	100 mg. daily (1 quart milk + 1 ounce brewers' yeast powder + liver or liver extract) Total daily caloric intake should be at least 4,000.	Undetermined.	10,000-50,000 units daily. (1 unit = activity of 1 mg. of standard solution of irradiated ergosterol or 0.025 micrograms of calciferol.)
Animal	Galbait liver oil. Percomorph liver oil.			Liver Kidney Spleen Lean meat Salmon		Cod liver oil. Halibut liver oil. Tuna liver oil (Percomorph). Vitamin D milk (see remarks). Summer milk contains 40 units per quart. Winter milk contains 5 units per quart. Irradiated milk contains 135 units per quart. Metabolized milk contains 400 units per quart. Fortified milk contains 400 units per quart.
Excellent Sources						

Vegetable	Yeast, brewers'	Yeast, brewers'	Yeast, brewers'	Yeast, brewers'	Yeast, brewers'	Vitamin D Bread contains 460 units per 24 ounce loaf or 115 units in 6 slices (average daily intake).
Synthetic or Artificial Concentrates	Carotene	Thiamin (synthetic). Ryzamin B (from rice polishings). Benax (germ layer from various cereals).				
Animal	Cod liver oil Butter Cream Cheese Egg yolk Milk	Ham, cooked Pork, roast Kidney Egg yolk Liver	Egg yolk Liver Cheese	Milk Codfish Haddock Egg		Irradiated ergosterol (vitosterol) Ultraviolet light
Vegetable	Raw carrots Broccoli Lettuce Tomato Spinach Water-cress Alfalfa	Whole grain cereals Peas Beans Hazelnut Walnut	Yeast Wheat germ Cottonseed flour	Beet greens Kale Potato Spinach Turnip greens Water-cress Wheat germ Pea, dried	Vegetables Celery Rhubarb Turnip Pea Spinach, cooked Fruits Citrus juice Lime juice Peach Pineapple juice Raspberry Strawberry Tangerine	

Veg. (Food Sources)

TABLE LXXIII—CONT'D

VITAMIN		VITAMIN A	THIAMIN (B ₁)	RIBOFLAVIN (B ₂)	NICOTINIC ACID (P-P)	ASCORBIC ACID (CEVITAMIC ACID, VITAMIN C)	VITAMIN D
Animal		Liver Kidney Oyster Clam Milk Milk, mother's	Brain Cheese Fish roe Milk Oyster				Butter Clam Milk Oyster
Vegetable		Vegetables Artichoke Asparagus Cabbage Celery Chard Corn (yellow) Pumpkin Panchelon greens Pea (green) Pepper (green) Squash String bean Sweet potato (yel- low) Carrot, cooked	Vegetables Asparagus Bean Cabbage Carrot Cauliflower Collard Lettuce Onion Parsnip Potato Spinach Tomato Turnip greens Water-cress	Spinach Kale	Banana Beet Cabbage Carrot Cauliflower Pear Lettuce Onion Tomato Turnip Wheat bran	Vegetables Bean (cooked) Beet Cabbage (cooked) Carrot Cauliflower Collard Cucumber Endive Lettuce Onion Pepper (green) Potato Pumpkin Spinach (cooked) Sweet corn Turnip greens Water-cress	
		Fruits Apricot Avocado Banana Orange Peach Pineapple Prune	Fruits Apple Banana Cantaloupe Date Grape Grapefruit Lemon Nuts Orange Peach Pineapple Prune Strawberry			Fruits Apple Banana Grape Grapejuice Pear Watermelon	

(Food Sources)

Remarks	A characteristic dermatitis due to deficiency, seen only in adults. Dry nutmeg grater dermatitis of outer thigh and forearm. May extend elsewhere.	Destroyed in cooking at high temperature. Boiling causes little destruction, but baking destroys 50%.	Food sources have not been extensively evaluated.	Some evidence suggests a relationship with the immunity mechanism. Avitaminosis C appears to diminish resistance to infection and to the action of diptheria toxin. Deficiency of the vitamin results in reduced complement titer.	Sunlight activates the provitamines. Irradiated ergosterol is vitamin D ₂ . This vegetable vitamin purified, is termed calciferol. Milk may be reinforced by irradiation ("irradiated milk"); by the feeding of irradiated yeast to cattle ("metabolized milk") or by the addition of vitamin D ₂ to milk, usually in the form of "fortified milk").
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these two observations in a series of experiments to determine whether cortin will protect sensitized animals with intact adrenals against anaphylactic shock. Using guinea pigs sensitized to purified egg albumin they found that cortin administered from 2 to 6 hours prior to the lethal shocking dose resulted in the survival of 9 to 16 pigs. Two others showed some protection. Of 16 control sensitized pigs shocked with the same dose but not receiving cortin, only two survived. Two weeks later the apparent protection conferred by cortin had disappeared. Cortin administered at other times than from 2 to 6 hours prior to shock appeared to exert little or no benefit. Cortin is best used prior to shock, adrenalin during shock.

The investigators found microscopic evidence in untreated pigs dying from shock, that there is an acute demand on the adrenal cortex during shock.

In anaphylactic shock the following blood changes have been described: lowered carbon dioxide capacity; decreased plasma volume; rise in serum potassium. The same changes occurred in experimental adrenal insufficiency. The injection of cortin tends to counteract all three changes. In adrenal insufficiency the low carbon dioxide capacity is associated with loss of serum sodium. Cortin increases serum sodium. In both anaphylactic shock and adrenal insufficiency it has been observed that an abundance of sodium salt is beneficial. In view of these observations Wolfrian and Zwemer suggest tentatively that cortin protects against anaphylactic shock by reason of its regulatory effect upon ionic and other changes dangerous to the health of the organism.

Clinical features.—Fineman (1933) described the use of suprarenal cortex extract as replacement therapy in the treatment of four cases of chronic bronchial asthma, on the theory of the existence of some degree of cortical insufficiency. The four patients had received prior treatment for from 1 to 27 months with little improvement. The extract was given in doses ranging from 0.5 cc. to 4 cc., three or four times weekly during the first month and once or twice weekly thereafter. Two received this treatment for four months, 1 for three months and 1 for six months. One was markedly improved, 1 moderately so, 1 slightly so and 1 was unimproved. Three of the 4 experienced distinct improvement in strength and appetite, with some gain in weight. There was no appreciable change in blood pressure or pulse rate.

Cohen and Rudolph (1935) attempted cortical hormone therapy with four asthmatics and concluded that the extract has no specific effect in patients with continuous asthma.

Wilmer and Miller (1936) treated 72 allergies refractory to other therapy with daily injections of cortical hormone in doses varying from 1 to 4 cc. The total amount given varied from 20 to 80 cc. In some, injections were given at longer intervals, up to once weekly. Forty-two per cent were improved, with complete relief in 13 per cent. The authors found no significant change in blood pressure. Thin, asthenic patients gained weight and in the majority there was an improvement in general health.

V. VITAMIN PRODUCTS

The situation here is somewhat analogous to that with the endoerines. Allergies, like others, may be deficient in one or another of the vitamins but vitamin deficiency has not been shown responsible for allergy. On the other hand, it is often important to consider vitamins when prescribing a rigidly limited diet to a food allergic, and to assure his receiving an adequate sup-

ply. Fortunately, enough is usually present in one or another food. Any single vitamin occurs in a sufficient variety of foods so that an adequate intake may usually be maintained with the diet alone.

One rarely encounters difficulty even in a person allergic to many foods in formulating a diet which does not contain sufficient vitamins. When this occurs, especially with vitamins B and C, the purified or synthetic vitamins may be prescribed.

Vitamin C. Ascorbic Acid.—Holmes and Alexander (1942) claimed marked relief in a high per cent of hay fever patients using large doses of ascorbic acid. From 250 to 500 mg. made the daily dose. A great deal of clinical evidence accumulated in succeeding years has not confirmed their report, and Friedlander and Feinberg (1945) found that hay fever patients have normal blood levels of ascorbic acid and that large doses produced blood saturation but did not affect the course of the allergic condition.

Vitamin D. Viosterol.—There is some evidence that vitamins, particularly vitamin D, may play an indirect part in the amelioration of allergic symptoms. Rappaport and his collaborators administered vitamin D as viosterol 10,000 X. This concentration represents 30,000 international units of vitamin D per drop. This was given in seasonal hay fever, from 2 to 10 drops daily commencing about ten days prior to the season. Sixty-eight cases received viosterol alone; 82.4 per cent experienced significant relief; 144 received viosterol and pollen hypsensitization, with 96.5 per cent gaining relief. Control medication with plain corn oil did not give relief. Symptoms of overdosage occasionally supervened. In their absence the dose was steadily increased from 2 drops to 10 drops daily.

In a later report (1936) Hathaway, Rappaport, et al., again reported better results in pollinosis from specific desensitization combined with massive doses of viosterol than from specific desensitization alone. They offer no explanation. The protective action of vitamin D is not correlated with changes in blood calcium or potassium or any other blood constituent.

Tremendous doses were required, a minimum daily dose of 200,000 U. S. P. units. About 50 per cent of cases required 500,000 units. The highest daily dose given for a short period was 3,000,000 units. Vitamin D treatment was started one week prior to the onset of symptoms. When started after symptoms had appeared, from 4 to 7 days' lag was observed before improvement resulted.

Overdosage leads to renal injury, with calcium deposition in the kidneys. This treatment should not be given to persons with nephritis or to elderly persons. Symptoms of overdosage of viosterol are urinary frequency, anorexia, abdominal distress, nausea and vomiting. They observed one person, allergic to corn oil, who reacted with abdominal pain and diarrhea.

In view of the fact that the large doses required for relief are believed to be not free from danger, this method of treatment has not gained acceptance.

VI. DRUGS DESIGNED TO MODIFY BIOCHEMICAL METABOLISM

Calcium

The calcium content of serum in health remains remarkably constant, around 10 mg. per 100 cc. Of this, 2 mg. exists as ionizable calcium with a total of 6 mg. dialyzable while the remaining 4 mg. is nondiffusible, combined with protein or lipids. The normal calcium requirement of a healthy adult is about 0.5 gm. daily. More is required during pregnancy and lactation. One pint of cow's milk provides sufficient calcium per diem in a readily assimilable form.

Early theoretical considerations which prompted the use of calcium in the treatment of allergic diseases were (a) that calcium deficit increased irritability of the autonomic nerve terminations; (b) that lime salt lessens permeability of tissue cells; (c) that calcium promotes metabolic balance of the salts of tissue fluids, especially calcium, potassium and sodium. As a consequence calcium salts have been employed in a number of diseases associated with hyperpermeability of the vessels, especially in Raynaud's disease, urticaria, angioneurotic edema, pleural and peritoneal effusion and asthma.

Several of the early investigations indicated that a low blood calcium level may occur in allergy. More recent and apparently more careful work has shown blood calcium to be normal. Lierle and Sage, for example, found normal blood values for calcium, phosphorus, potassium and protein, in asthma. Calcium, phosphorus and potassium values in the spinal fluids of asthmatics were likewise normal. Furthermore it has recently been shown that determination of total calcium is of little significance; that ionized calcium should be measured. Studies of ionized calcium show it to be normal in allergy. Although calcium therapy is still used occasionally, after the patient has failed to respond to the more rational procedures, it is usually quite ineffective. Occasionally a patient will appear to improve surprisingly, especially after intravenous calcium, but it is difficult in such sporadic cases to prove that the improvement was not coincidental.

Study of calcium therapy continues. For example, Culphey and Solomon treated 15 cases of serum sickness with large doses of calcium gluconate intravenously and intramuscularly, comparing the results with an equal number not so treated. Using both subjective and objective criteria they found the duration of illness roughly half as long in the former. Kallos and Kallos-Deffner, using the Dale uterine strip technic, concluded that calcium prevents this form of anaphylactic reaction and promptly terminates it if it has already commenced.

On the other hand, Tainter and Van Deventer found no protective anti-edemic action of calcium and parathyroid extract in experimentally produced edema except in the presence of circulatory depression. This observation tends to controvert one of the chief reasons for calcium administration.

Calcium is poorly absorbed from the intestinal tract. When given intravenously, the gluconate is preferable to the chloride. It is not necrotizing if extravasated. Both salts may produce a sensation of extreme heat or burning which spreads over the entire body. This is a typical calcium action and may be avoided in great measure by very slow injection. The intravenous dose is 1 or 2 gm. (10 cc. of a 20 per cent solution). Calcium gluconate may be given intramuscularly but the chloride may not, on account of its necrotizing action.

Chief interest in calcium, from the viewpoint of allergy, as in the vitamins, lies in the assurance of an adequate calcium intake. This need not be considered except with those who must avoid milk. When milk is prohibited, it is a safe precaution to prescribe a heaping teaspoonful of calcium gluconate in water morning and evening or a di-calcium phosphate wafer once or twice daily. However, it should be noted that Rudolph (1936) reports that 13 of 36 chronic allergies who had not responded to previous allergic therapy, when given di-calcium phosphate, 1 gm. thrice daily over a period of a year, were distinctly improved at the termination of the survey. Only two cases experienced ill effect, paroxysms of diarrhea, nervousness and unpleasant

taste. He believes that calcium therapy is frequently effective in bringing about clinical improvement in allergic disorders and that it should be given indefinitely as part of the regular program to any person suffering from an allergic disorder.

While children may be deficient in phosphate, adults are rarely so. Meat usually provides enough. When calcium is given sufficient vitamin D should be added in one form or another to promote intestinal absorption. Tablets of Calcium Phosphate Compound with viosterol 10-D are generally available. These contain 2.6 grains of calcium. Six tablets daily should provide an adequate calcium intake (1 gm.). Calcium gluconate and calcium lactate molecules are larger. It requires 11.2 gm. of calcium gluconate and 7.7 gm. of calcium lactate to provide 1 gm. of calcium. Normal daily requirements are 0.5 to 1 gm. An adequate daily dose of calcium carbonate (chalk), calcium gluconate or calcium lactate is 10 to 15 gm.

Acid Therapy

There is some evidence suggesting that the allergic attack may be associated with low-grade blood alkalosis, or, more properly, a slightly decreased hydrogen ion concentration. A number of investigators have also described gastric subacidity in allergies. For these reasons several investigators have recommended the administration of dilute hydrochloric acid or dilute nitrohydrochloric acid in hay fever and the other allergies. Hydrochloric acid diluted 1:1,000 or 1:1,500 has been recommended intravenously for relief of acute symptoms. The writer has tried this in a few cases and has seen no deleterious results and no evidence of benefit.

Even the ketogenic diet had a short vogue, its object being to create low-grade acidosis. Alexander has analyzed the effects of the ketogenic diet in adults with bronchial asthma, finding no evidence that ketosis had a beneficial effect on the severity or duration of the paroxysm. Peshkin and Fineman had previously reported good results in children. The ketogenic diet is little used in allergy at present.

Wilson and his collaborators have studied the possible alkalotic tendency. They placed 55 scarlet fever patients who had had antitoxin on a ketogenic diet; 97 controls who had also received antitoxin were placed on an antiketogenic diet, with adequate carbohydrates; 80 per cent of the latter developed serum sickness while only 47 per cent of those on ketogenic diet did so. Thirty-eight per cent of those on ketogenic diet developed generalized urticaria compared with 75 per cent on antiketogenic diet. Duration of urticaria among those on ketogenic diet averaged 35 hours; among the control group, 57 hours.

The writers observed that when hydrochloric acid was given, in addition, to those with ketosis, results were slightly better. They conclude that ketosis tends to reduce the frequency and severity of serum sickness.

The giving of hydrochloric acid in the presence of gastric subacidity might appear rational, but Loveless in a study of 138 children and adults found no correlation between allergy and a lowered gastric acidity. Indeed the mean free acid was higher in the allergic group than in the normals. Intensive hydrochloric acid therapy did not influence the acid-base balance nor did it result in any impressive clinical response.

Glucose

The creation of a high blood glucose may be looked upon as diametrically opposed to the production of ketosis. Glucose has found much wider favor in allergy than the latter. Intravenous glucose may also be looked upon as the reverse of insulin administration which has been recommended in asthma by at least one author.

A high glucose diet in asthma was suggested by Osman in 1929. In 1932 Stoesser studied an asthmatic child who gave a remarkably constant asthmatic response to a fixed-size feeding of codfish. He could produce attacks of quite constant duration and severity at will by feeding the allergen. The ketogenic diet gave no protection against these attacks, while 25 per cent glucose solution intravenously gave definite relief, the attacks being less severe and of shorter duration. When given shortly after codfish ingestion, it prevented reaction. The early administration of glucose orally was of little value, but when given after the attack was well developed, it did shorten the course. Severe asthmatic attacks required intravenous glucose, while some of the mild attacks were controlled with oral glucose solution. In this case intravenous glucose appeared to be just as effective in controlling the allergic reaction as adrenalin. An abundant water intake at the same time appeared to help.

Matzger also reported good results with 500 cc. of 20 or 25 per cent solution or 1,000 cc. of 10 per cent solution. He suggested that the hypertonic solution in the vein may determine a flow of edema fluid from the tissues into the blood stream.

Black finds that more than half of asthma and hay fever patients have fasting blood sugar values below normal together with an increased sugar tolerance. This is of interest in view of the relative infrequency of asthma in diabetics and the occasional good results from the treatment of asthma with intravenous glucose. Rackemann was unable to confirm the finding of low blood sugars. He believes there is no variation from the normal.

Lepak found in 4 intractable asthmatics that daily intravenous glucose injections (50 cc. of 50 per cent solution) gave a good measure of relief. The action was slow, requiring several days of injection.

VII. HYPNOTICS AND ANESTHETICS

Early in the study of experimental anaphylaxis Besredka, also Richet, observed that anaphylactic shock was prevented or diminished under ether anesthesia. It was also observed that rupture of hydatid cyst, with spilling of the contents onto neighboring tissues, produced anaphylactic shock unless the patient was under general anesthesia.

Ether

Asthmatics often experience relief for variable periods following surgical operation. One cannot state categorically that this is due to the anesthesia because similar experiences follow acute infections and some persons observe exacerbation of symptoms following surgery.

Vallery Radot and his associates report 11 cases in whom severe and persistent asthma was relieved following incidental operation. That the anesthesia was not the explanation is indicated by the fact that some were operated upon under local anesthesia. They also report 6 cases in which incidental

surgery started asthma or produced asthma in cases that had previously had vasomotor rhinitis. Their conclusion is that surgical intervention could conceivably modify the state of the vegetative nervous system and could consequently initiate or stop the crises.

These observations indicate at any rate that surgery under general anesthesia is not contraindicated by the anaphylactic state, even when the symptom is respiratory and the operation is on the respiratory tract. Andre and Grove concluded, from a series of 204 tonsillectomies and radical sinus operations under general anesthesia, that the latter is as safe in allergic patients, even the severely asthmatic, as in others, provided the patients are properly selected; provided the operative method combines light anesthesia, carbon dioxide and oxygen; and provided careful postoperative treatment is carried out. They observed no pulmonary complications.

Kahn deliberately induced ether anesthesia in four patients with intractable asthma. They were temporarily relieved, but not for as long as sometimes happens after surgery.

Swineford described a patient who when apparently moribund, with vital capacity of 200 cc., was given nitrous oxide anesthesia. Within ten minutes her vital capacity had increased more than 1,000 cc. Ten months later she had had no recurrence of severe asthma.

Maytum suggested the use of ether in oil by rectum in asthma (1931). Kahn also recommends this, the average adult dose being from 5 to 7 ounces of a mixture of equal parts, given over a twenty-minute interval. A number of investigators have reported success in the relief of the asthmatic attack with ether in oil. The writer prefers one part in three or four of ether in oil.

It should be borne in mind that Waldbott has described what he believes is allergy to ether, with asthma or even anaphylactic shock.

Although there is experimental evidence that ether anesthesia protects against anaphylactic shock, Quill (1937) reports an anaphylactic death in a person given prophylactic tetanus antitoxin while under ether. He reviews the literature, citing a number of examples of shock under anesthesia. Obviously, then, one cannot routinely give potential allergens under general anesthesia in the assumption that even if the patient is sensitized there will be no serious reaction.

Avertin

Fuchs (1937) advises avertin (tribromethanol) administered rectally for the production of anesthesia. This is dissolved in "avertin fluid" (amylene-hydrate) and given slowly with a funnel or syringe attached to a male catheter. The dose is 60 to 70 mg. per kilo body weight. Muscular relaxation usually occurs within ten or twenty minutes although occasionally as long as an hour is required. The patient usually sleeps from one to six hours and is relieved of his asthma for days or even weeks. Refractoriness to epinephrine may disappear after this treatment. In a series of 25 cases Fuchs observed no untoward results.

Beecher (1938) has reported 10 deaths due to avertin (tribromethanol) with amylene-hydrate among 3,934 avertin anesthetics. He concludes that the drug is more toxic than chloroform.

Urethane

Farmer (1937) found that urethane, like ether, prevents the contraction of smooth muscle in the anaphylactic reaction and suggests that this is responsible for its beneficial effect in anaphylactic shock in the guinea pig and asthma in humans. Morphine on the other hand constricts bronchial musculature, thereby exaggerating the shock reaction.

Farmer (1939) used ethylurethane in 30 cases of bronchial asthma, giving doses of 1 or 2 gm. dissolved in water with a total of not more than 4 gm. daily. It was not given longer than for four or five successive days. There were no untoward effects. In approximately 50 per cent of cases symptomatic relief was prompt (15 to 30 minutes) and apparently comparable to that from ephedrine.

The adrenalin-fast patient.—Fortunately intractable status asthmaticus is sufficiently rare. When it becomes severe, the patient as a rule no longer responds satisfactorily to epinephrine administration. He becomes "adrenalin-fast." It would appear that almost any measure that will terminate the persistent attack even temporarily breaks the continuity of the unknown mechanism responsible for constant symptoms. Thereafter the patient again responds in a normal manner to adrenalin and often to other customary drugs. The disappearance of "adrenalin-fastness" has been described as following avertin, aminophylline by suppository or intravenously, helium and oxygen, and ether.

It would appear that sedation even to the point of general anesthesia is of benefit in interrupting the asthmatic state. No pharmacologic explanation is forthcoming. Relief of anxiety and emotional tension probably plays a part but it seems probable that also a more direct pharmacologic factor is bound up with the phenomenon of general relaxation.

Sedatives

Sodium bromide and chloral hydrate may be used alone or combined for sedation. Paraldehyde may be used orally in 4 to 10 c.c. doses or in double these amounts when injected rectally. It is a very objectionable tasting drug, but sometimes gives excellent relief.

The barbiturates may cause allergic reactions, and this should be kept in mind. However, they are frequently of considerable help in addition to the use of epinephrine or the ephedrine substitutes in the restless, sleepless patient.

VIII. MISCELLANEOUS

Aspirin

In the occasional case aspirin, like coffee, gives relief which is every bit as effective as that from adrenalin. The mechanism is unknown. Such cases are not frequent. Before prescribing aspirin one should be certain that one is not dealing with a case of aspirin allergy. For those who do tolerate aspirin Duke recommends the trial of large doses, 15 or 20 grains if necessary, before concluding that the patient will not respond to aspirin.

Whisky

Whisky is in the same category with aspirin and coffee. Many find that alcohol increases symptoms.

Relief in those patients in whom large doses of alcoholic beverages appear beneficial may be due to the same mechanism which is said to be active in general anesthesia. Besredka (1930) stated that alcohol as well as ether, chloroform, and ethyl chloride, suppresses the anaphylactic reaction.

Expectorants

Iodides.—In allergy, iodides are used principally for relief of asthma, results being attributed apparently to increase in bronchial secretion, facilitating raising of the thick tenacious sputum. There is no action on bronchial musculature. That iodides act beneficially in many cases is indicated by the fact that some form of iodide is a constituent of nearly all asthma nostrums, sometimes the only active constituent. Very occasionally an asthmatic will respond to sodium iodide or potassium iodide who has failed to respond to all other therapeutic measures. In the writer's experience there is no preference between the two salts except when used intravenously, then the sodium salt should be employed.

Since the iodides are readily absorbed, there is little logic in their intravenous administration except when digestive disturbance follows oral dosage. On the other hand, some cases appear to do better with intravenous administration of one gram of sodium iodide in 10 per cent solution. Theoretically it seems possible that iodide carried directly to the lungs without passage through the liver might exert a rather different action. No experimental work has been done on this question.

Iodism is a side-effect of iodine medication which sometimes necessitates discontinuance of this therapy. Some consider this allergic and it is true that not all persons exhibit iodism. On the other hand, symptoms are rather different from the more common allergic manifestations. These include catarrh of the upper and lower respiratory passages, edema of the nasal mucosa, sneezing, profuse rhinorrhea, conjunctivitis, lachrymation, edema of the eyelids, headache due to swelling of the sinus mucosa, edema of the larynx occasionally with ulceration, salivation, and various forms of skin eruption including erythema, papules, pustules, bullae, purpura, simulating a large number of dermatoses. Iodide should never be given intravenously without preliminary trial by mouth to rule out idiosyncrasy. This is usually manifested by some pain in the region of the parotid gland following ingestion.

Sodium and potassium iodide are readily soluble, in the proportion of one grain to one drop. They are usually prescribed in saturated solution, as potassium iodide 60 grams in distilled water or peppermint water q. s. to make 60 cc. As a rule the initial dose is 15 drops (15 grains) before or after meals, to be increased gradually if necessary. The onset of iodism requires temporary discontinuance.

Ammonium chloride may be used in an expectorant cough mixture or used as a substitute for iodide when the latter, for any reason, is not desirable.

Syrup of Ipecac has been found quite useful in children as an expectorant or, often as an emetic in the asthmatic attack.

Penicillin

With the widespread use of penicillin, it is to be expected that it would be used in the treatment of asthma. It is, of course, of no value except in those cases associated with bronchial infection but, in these cases, is believed by many

workers to be very helpful. It has been used quite frequently in the form of an aerosol, and can be given in large amounts with apparent benefit in many instances and with no evidence of irritation if properly administered (Barach, Abramson, Prigal).

Sulfonamides

The statements made regarding penicillin are applicable to the sulfonamides. Sulfathiazole and sulfadiazine have been used orally and as aerosols, and have been believed to be of help in the infected cases.

Privine

Privine is 2-naphthyl-methyl imidazoline. It is a colorless, crystalline substance readily soluble in water or saline solution. As a hydrochloride it is used as a vasoconstrictor and gives prompt, marked, and prolonged relief from nasal blocking. As a 0.1 per cent solution it is isotonic, and its pH is 6.2.

This drug has been widely used for the relief of nasal symptoms in pollinosis or perennial allergic rhinitis. A considerable number of persons become quite dependent upon it and use it with increasing frequency with an increase of the symptoms which it is used to relieve. These patients are promptly much improved by stopping the use of the drug.

Estivin

Estivin is a proprietary preparation rather widely used as drops for relief of conjunctivitis accompanying hay fever. According to the manufacturers it is a liquid preparation of *Rosa gallica*. *Rosa gallica* is a variety of sweetbrier.

IX. NONSPECIFIC DESENSITIZATION

There was more interest in this phase of allergic therapy formerly than now. Early investigations had indicated that antianaphylaxis could be produced by certain nonspecific measures, measures other than the administration of sublethal doses of the specific antigen. Attempts to apply this in clinical allergy led to such procedures as "*nonspecific desensitization*" with peptone, milk, shock therapy with typhoid vaccine, etc. Since these measures have in general been inefficacious and since they do not desensitize, recent discussions have used the term *nonspecific treatment*. This is still too broad a term since it would properly include all drug therapy previously described.

Wells listed substances reported as producing nonspecific transitory reduction of anaphylactic reactivity. These included peptone, trypsin, various inorganic salts including sodium chloride, urine, foreign proteins other than those used in sensitizing and sodium oleate. Most of these have been tried clinically without notable success.

Histamine

Histamine therapy is really the only procedure that might logically be considered as nonspecific desensitization.

Victor C. Vaughan (1913) found that the protein poison (unpurified histamine) caused anaphylactoid symptoms on first injection without requiring a previous sensitizing injection. In other words, it acted as a true poison. He further observed that repeated injections of small but gradually

increasing dosage produced an increased tolerance to the poison, much larger doses causing no consequent symptoms. This was quite different from desensitization and indicated an increased tolerance to a true poison, somewhat analogous to morphine, nicotine, arsenic and alcohol. Larger doses still caused symptoms.

Assuming, in terms of the Lewis theory of the H-substance that histamine or a histamine-like substance is the poison liberated internally in the allergic reaction, one might attempt to increase tolerance to this end-product by subjecting the tissues to more or less continued exposure thereto.

Bray (1931) reported successful desensitization of a case of allergy to cold following a course of histamine injections. Similar good results were reported in cold allergy by Horton, Brown and Roth. Collens et al. (1934) treated an insulin allergic with histamine, with increasing injections commencing with 0.1 mg., treatment being given thrice weekly. Insulin reactions had diminished after thirteen doses. After another five the patient could take insulin without reaction. The highest dose of histamine was 1 mg. Unpleasant side effects following these large doses include flushing of the face, sneezing, sweating, headache, dizziness and fall in blood pressure. It seems illogical to treat insulin allergy with histamine injections if desensitization with insulin accomplishes the same purpose.

Thiberge (1935) reported success in the histamine treatment of asthma and hay fever in cases that had not responded to other methods. He accomplished this with small intracutaneous doses.

Dzsinich reported complete cure in 12 of 15 asthmatics after a series of histamine injections. The first was intracutaneous. If there was no untoward reaction subsequent injections were subcutaneous. One hesitates to accept the report of complete cure of asthma with any of the methods today available, including histamine. Later, with Paul, Dzsinich reports encouraging results following the combined use of histamine and magnophylline (theocin) in asthma, urticaria, vasomotor rhinitis and vernal conjunctivitis.

Alexander (1940) reported the treatment of urticaria with intravenous histamine, and Horton (1941) discussed its use in headaches. In 1939 Horton described a new syndrome of vascular headache which he termed "histaminic cephalgia" and for which he claimed specific desensitization by histamine. Since that date histamine has been advocated for all forms of allergic manifestations and its use both intravenously and hypodermically has been widespread. Horton has been very enthusiastic about the results of such treatment, and believes it is the method of choice in a large variety of conditions. The experience of many workers is that histamine will sometimes give dramatic relief from urticarias, histamine cephalgia, and less frequently in other conditions. Treatment probably consists of building a tolerance rather than a true desensitization and this tolerance, if obtained, appears to be short lived.

Administration.—Histamine hydrochloride, 1:1,000 dilution, is available in 1 cc. ampules. Each ampule contains 1 mg.; 0.1 cc. contains 0.1 mg. When using histamine the writer gives daily injections commencing with 0.1 mg. and increasing by 0.1 mg. each time until improvement is observed or symptoms of overdosage, especially headache, appear. The majority experience these uncomfortable symptoms at about 0.4 or 0.5 mg. Thereafter the dose is kept constant, for several injections, after which further increases may be tried

to determine whether tolerance is increased. If symptoms are relieved, the dose is held constant and the interval gradually increased to twice weekly or once weekly if possible.

Results in my experience have not been particularly encouraging. We have used the method in urticaria, asthma and allergic coryza. To be sure, we have subjected our most difficult cases to it, those which have not responded to specific therapeutic measures. Endermal injections as recommended by Thiberge might well be tried.

Since there is considerable waste when 0.1 cc. is used from a 1 cc. ampule, we customarily empty two or three ampules, by means of a sterile syringe and needle, into a sterile rubber capped extract vial, from which the proper dose may be withdrawn as needed.

Benadryl

With the rather general acceptance of the theory that histamine is the result of the antigen-antibody reaction in allergic reactions and that histamine accounts for the symptoms resulting, there has been a great interest in the use of histamine itself and substances which might interfere in some way with its action. Histaminase was advocated—without adequate physiologic basis—and found wanting. Histamine-azo-protein was tried with little success.

The first synthetic antihistaminic drugs were produced by the French who introduced antergan (N' phenyl-N' benzyl-N-dimethylethylenediamine) and, a little later, neoantergan (N-p-methoxy-benzyl-N-dimethylamino ethyl aminopyrine) which was less toxic and came into general use in France.

Benadryl (β -dimethylaminoethyl benzhydryl ether) is a histamine antagonist as may be shown by inhibition of bronchoconstriction in the guinea pig, of contraction of the intestinal strip, and of the fall in blood pressure in the dog and cat following histamine. It greatly modifies or prevents anaphylactic shock. It inhibits histamine skin reactions and those due to antigen-antibody reaction. It has been found very effective in the relief of urticaria, serum sickness, urticarial or "serum sickness" type of drug reactions, and may be of much help in relieving the symptoms of pollinosis. It does not do so well with the perennial allergic rhinitis cases, and few asthmatic persons are helped by it.

There are several unpleasant side-effects of the drug. Many persons develop an uncontrollable somnolence while others complain of confusion, dizziness, numbness, nausea, and other symptoms in less frequency. These effects lessen the usefulness of the drug materially.

Doses of 50 mg. may be used three or four hours apart with smaller amounts for children. Larger doses are seldom of more benefit.

Pyribenzamine

Pyridyl-N-benzyl-N-dimethylethylenediamine is quite similar in action to Benadryl. It is more effective in neutralizing histamine. It probably does not cause quite as many unpleasant side effects as does Benadryl. It is an interesting observation that a patient who does not get satisfactory relief from one of these drugs may get it from the other and vice versa. It seems too that prolonged use of either drug may lead to a certain amount of tolerance.

Other drugs of this character with slight changes in chemical structure are now being made and are undergoing clinical trial. It may be that a much more effective preparation with few or no side-effects may be available. There is nothing to indicate, however, that this type of drug will offer more than temporary relief from symptoms and will always be limited in its usefulness.

Urinary Proteose

In 1929 Oriel reported the presence of a substance which he termed "proteose" in the urine of persons with acute allergic episodes. This substance produced positive skin reactions which could be passively transferred. According to Oriel and Barber (1930) the "proteose" could be used successfully in desensitization. They felt that proteoses obtained from different persons were specific and suggested that the original antigen might combine with some reactive substance in the liver, producing a secondary, changed antigen which, however, still possesses antigenic specificity. Darley and Whitehead (1931), also Mills and Martyn (1933) reported good results from treatment with autogenous urinary proteose.

While Trasoff and Meranze (1933) believed that they isolated something from the urine which corresponds to the proteose described by Oriel, they were unable to demonstrate any specificity in the reaction or to achieve relief following therapy. Freeman and Bray in England reached similar conclusions.

Vaughan (1933) failed to obtain clinical improvement in pollinosis with so-called proteose therapy; failed to obtain specific positive skin or P-K reactions; and was unable to demonstrate an increase in total urinary nitrogen.

Tuft and Brodsky (1933) found that a substance resembling proteose is present in normal urine, rather more so in allergic urine, but that it is of no allergic significance.

Black and Shelmire (1934) concluded that what appears to be proteose is, when present, probably the unchanged antigen rather than some new substance. The same procedure which extracts this so-called proteose will extract unchanged pollen antigen from the urine. They found that "proteose extracts" presented the characteristics of weak pollen solutions.

Schube (1934) reported one case of urticaria in which very good results were obtained.

Cohn (1937) found that urinary "proteose" did not give positive skin reactions in 5 children with asthma. Passive transfer was negative. Therapy was ineffective.

Libman and Bigland (1937) conclude that the erythematous skin reaction is nonspecific, toxic in origin; that therapeutic benefit in cases of asthma is about the same as that obtained with peptone; that peptone treatment is preferable on account of its simplicity. They do however report encouraging results in cases of urticaria and suggest that further investigation is warranted. These last authors provide a comprehensive review of the literature.

Technic.—The "proteose" is extracted as follows:

Four hundred cc. of fresh urine is required. If there is to be any delay, the urine should be voided into a sterile bottle containing 0.5 cc. of c. p. chloroform. This is made acid to Congo red (pH_3) with dilute sulfuric acid. The acidified urine is then shaken with 100 cc. of c. p. ether in a separatory funnel. After separation the lower layer is run off and discarded. To the remaining layer absolute alcohol is slowly added with constant shaking to a total of 100 cc. A precipitate forms which is drawn off into a centrifuge tube, washed with absolute alcohol and centrifuged. This is repeated three times. Supernatant fluid is poured off and the precipitate suspended in sufficient N/10 NaOH to make it barely alkaline. It is then transferred to vaccine vials and made up to 10 cc. with Locke's solution. This suspension is designated 1:1,000 dilution. Serial dilutions are made from this stock vial.

PART XVI

THE ALLERGIC DISEASES*

Asthma is doubly capricious; the disease in general is capricious, and each case is capricious in itself.

—HENRY HYDE SALTER.

CHAPTER LXXII

ASTHMA

The writer is in agreement with Alexander, that the term bronchial asthma is unfortunate, since all true asthmas are immediately bronchial in origin. It represents another of those etymologic failures in medical diction which at times obscure correct perspective.

Historical notes.—The term asthma “I gasp for breath” was used by Hippocrates (460-377 B.C.) to signify “hurried breathing.” It would seem that a disease presenting such startling subjective and objective symptoms, sudden onset, severe course, sudden termination without apparent residual symptoms, and regular or irregular periodicity, could not fail to have been recognized as a disease entity by the early Greek observers. Nevertheless it was not until toward the end of the seventeenth century that the word was used in any other sense than as descriptive of any person “gasping for breath.”

Celsus (first century A.D.) employed the term to indicate a degree of shortness of breath, *dyspnea* implying a mild symptom, *asthma* more severe, and *orthopnea* the most severe form. Aretaeus, his contemporary, first described the asthmatic paroxysm, calling attention to this very characteristic feature of the disease. Galen (A.D. 130 to 201) did not include this concept in his records. It was therefore lost to medicine for over 1,500 years. During this long interval asthma was synonymous with panting for breath and was a grade between dyspnea and orthopnea.

First period.—With the renaissance of medicine, van Helmont (1577-1644), who was himself asthmatic, first called attention to the spasmodic element, sudden attacks with intervals of freedom. Thomas Willis (1621-1675) recognized the peculiar episodes of shortness of breath and the absence of evidence of bronchial or pulmonary disease at autopsy. Credit for the understanding of asthma as a disease entity is accorded to Willis. He described two types, the pneumonic and the convulsive, which today we may recognize as chronic, persistent, and acute episodic.

Sir John Floyer (1698) states in his “treatise of the asthma” that he himself “had suffered under the tyranny of the disease for at least thirty years.” An acute observer, he gave a vivid account of the asthmatic paroxysm and of the many causes of the acute attack, in his own experience and that of his patients. Floyer attributed the disease to “straightness or constriction of the bronchi.” Like Willis he divided asthma into two types, the “continued” and the “idiopathic, convulsive, or periodic flatulent.”

Following the epochal work of Willis and of Floyer which received wide acceptance for a time, there developed a tendency to revert to the conception of the ancients, all manner of difficult breathing being called asthma, usually with the addition of descriptive adjectives such as nervous, arthritic, cardiac, abdominal, plethoric, dry, humid and convulsive. Nearly eighty years after the time of Floyer, Cullen (1777) again recognized spasmodic asthma or *asthma convulsive* as an entity, pointing out its hereditary tendency, nocturnal frequency, the effect of weather, the intervals of freedom, and ascribing the disease to spasmodic

*Due to space limitations the writer makes no effort to present a complete analysis of the history, etiology, pathology, diagnosis and treatment of each of the allergic diseases. This is scarcely necessary since the information is available in standard texts on internal medicine. The discussion will therefore be limited in great measure to those aspects of the diseases which touch upon allergic practice and to developments of very recent years, many of which have not as yet appeared in the more general texts.

constriction of the bronchial muscle fibers. Finally Bree (1803) contributed a most comprehensive essay in which he recognized the continuous and discontinuous forms and added the concept that the primary cause is an exudation into the bronchi, that dyspnea represents an effort to expel irritating material.

This brings us to the termination of the first phase of the recognition of asthma as a disease entity, and suggestions concerning its pathologic physiology.

Second period.—The second period opens with the observations of Laennec (1819) who brought to the study of chest diseases his newly discovered method of auscultation. He showed that many cases of supposed asthma were actually due to gross and permanent cardiac and pulmonary lesions, discoverable during life and demonstrable after death. Shortness of breath is but a symptom which may be due to many causes. Among the causes he distinguished an affection, characterized by paroxysmal dyspnea without demonstrable associated organic lesions, in which during the free interval no evidence of disease whatsoever could be found on auscultation. He reasoned that the cause of asthma must be spasm of the muscles of the bronchi. Laennec may be said to have established the existence of idiopathic asthma. He believed the disease to be primarily a neurosis.

It is this concept which dominates the second phase of the history of asthma. Longuet (1842) showed that stimulation of the distal end of the cut vagus would produce bronchial constriction. The observations of a number of workers now contributed to the establishment of a nervous etiology. Among them should be mentioned Romberg, Bergson, Ramadge, Andral, Hyde Salter (1860) and Trousseau, the great French clinician of the middle of the nineteenth century who regarded asthma as a diathetic neurosis dependent upon spasmodic constriction of the bronchi and interchangeable, in the diathesis, with eczema, rheumatic infection, gout, gravel, hemorrhoids and periodic headaches.

Not all writers accepted the concept of bronchial spasm. In the latter half of the nineteenth century there were three principal theories: (1) bronchial spasm; (2) spasmodic contraction of the diaphragm at maximum depression; (3) sudden turgescence of the bronchial mucosa, as suggested by Bree. Three other theories had some support: (4) a morbid diathetic condition of the blood influencing at one time the skin, at another the mucous membranes; (5) mechanical irritants in the bronchi such as Charcot-Leyden crystals, Curschmann's spirals, eosinophile cells; (6) primary pathology elsewhere in the respiratory tract, especially nasal polyps.

The opening of the twentieth century found idiopathic asthma quite generally considered as a neurosis. This is reflected in the reviews which appeared in the three leading systems of medicine of the time: *Twentieth Century Practice of Medicine* (1896); *Notnagel's Encyclopedia* (1902); and *Osler's Modern Medicine* (1907). However even though the nervous element was emphasized, the importance of extrinsic excitants in the precipitation of attacks was recognized. The following etiologic agents were described, the mechanism being dismissed with the simple explanation of "idiosyncrasy": pollens, rose, violet, mignonette, ipecac, handling of fresh coffee beans, oak wood, mattresses, privet, various scents, the odor of a cat or a piece of fur, climatic changes, house dust, wood smoke, the ingestion of certain foods, feathers, the smell of horses, lamp soot, oats. Trousseau himself had asthma from the dust of oats.

At that time the age factor was well recognized. Hyde Salter (1863) found that 31 per cent of his asthmatics commenced with symptoms in the first decade, 12.8 per cent in the second and 80 per cent before age 40. Berkart (1889) found an hereditary tendency strongly marked in 16 per cent. At that time it was recognized that asthma was not a common hospital disease, occurring more among the more well-to-do classes, preachers, lawyers, teachers, etc.

Third period.—The third or present period of the study followed the early investigations in anaphylaxis and may be said to date from 1910, when Auer and Lewis demonstrated bronchospasm as a constant finding in the lungs of guinea pigs dead from anaphylactic shock, and Meltzer put forward the suggestion that asthma might eventually be shown to be an anaphylactic disease.

Pathology

The lungs and bronchi.—The first necropsy report on asthma was by Van Leyden in 1886. By 1937 a total of 50 necropsies had been reported, a number of which have not been accepted by pathologists as being deaths from true bronchial asthma. Lamson and Butt (1937) added 48 cases bringing the total to nearly 100. Several of the reports have included detailed analyses

of the literature. One of the most comprehensive was that by Huber and Koessler. Kountz and Alexander, Michael and Rowe have contributed excellent discussions. Walzer carefully analyzed the 33 reports up to 1930 and Lamson and Butt have brought the discussion up to date.

Death from asthma during an acute attack is relatively infrequent. The paucity of available material has prevented opportunity for extensive study of the tissue pathology.

Characteristic findings. What changes have been observed in the lungs and bronchi may also occur in other diseases. There is therefore no strictly characteristic pathologic picture, but certain changes are observed with such frequency that they may be termed characteristic. These are as follows:

(a) Emphysema.

(b) Increased thickness of the bronchial wall with narrowing of the lumen.



Fig. 298.—Pathology of asthma. Contracted bronchiole with evidence of muscular hypertrophy and low-grade cellular infiltration.

(c) Increased thickness and infolding of the mucosa.

(d) Excess mucus in the lumen, sometimes with plugs of thick tenacious mucus and fibrin.

(e) Dilation of the smaller bronchioles and alveoli.

(f) Cellular infiltration (eosinophiles, plasma cells and lymphocytes), of the mucosa, submucosa, mucous glands and, at times, the musculature.

(g) Thickening and hyaline degeneration of the basement membrane.

(h) Hypertrophy of the bronchial musculature.

(i) Degeneration of the mucous glands.

Alexander lists the most important and characteristic of the above changes as: widened basement membrane, eosinophilic infiltration, widened submucosal layer, hypertrophy of muscle and degenerative mucous glands.

Macdonald reports that among 3,690 autopsies at the University of Michigan Hospital since 1896, only 8 were for bronchial asthma. Five of these died either

immediately after a paroxysm or from cardiac failure or from asphyxia. The other 3 died from intercurrent infection.

The most constant findings were: thickening and hyaline changes of the basement membrane of the bronchi; eosinophilia; varying hypertrophy of the bronchial musculature; bronchial sacculations occurring through the mouths of the mucous glands; and epithelial changes such as hypertrophy and metaplasia. Ventricular hypertrophy was almost a constant finding.

Hansen (1936) emphasizes that asthmatic deaths are more frequent than the literature would imply. Although at the time of his report there were 52 cases in the literature, autopsy records for twenty years at the University of Minnesota contained 35 such records. He reviewed 15 fatal cases of asthma in the University records 1933-1934. In 4 autopsies showed asthma to have been the cause of death. Of the remainder, 7 died of pulmonary infection, 2 of

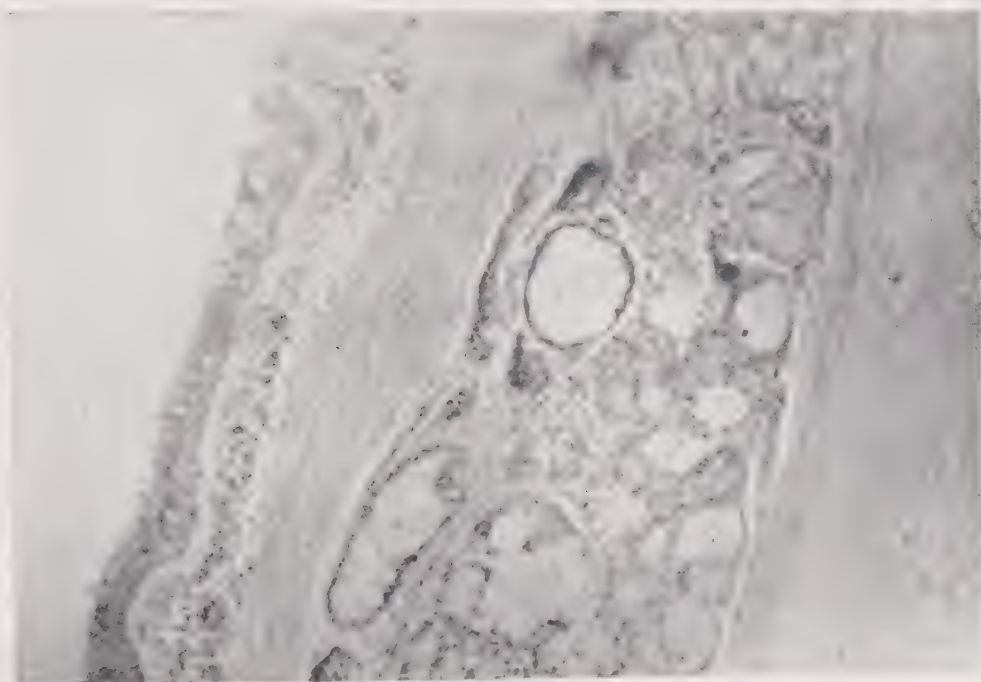


Fig. 299.—Pathology of asthma. Note hyaline thickening of basement membrane and prominence of bronchial musculature. In this case the bronchial tree was dry, there being minimal mucous plugging. Note absence of plug in lumen at left.

nonpulmonary accidents, 1 of right heart failure, and 1 of emphysema. Extensive fibrous pulmonary adhesions were observed in 6 of the 7 with pulmonary infection and in the 2 with death from nonpulmonary accidents. Since all of these were clinically chronic asthmatics, Hansen raises the question whether the asthmatic changes can, through superimposed bacterial infection, lose their typical characteristics and end in a chronic bronchitis or pleuritis.

Mucous plugs.—We have seen in the historical review that two of the three leading theories held that asthma was due either (1) to spasm of the bronchial musculature or (2) to swelling of the mucous membrane, with increased secretion in the bronchi. Even today observers disagree concerning the relative importance of these factors. Probably the majority feel that both play a part but some attach much greater significance to bronchial secretion than to bronchospasm.

Steinberg, from experimental evidence and autopsy studies, concluded that the asthmatic attack is not due primarily to bronchial constriction but to plugging of the bronchi with mucus. The mucus results from hypersecretory activity of the bronchial glands. The degree and duration of the attack depend upon the quantity of secretion, the extent of bronchial plugging and its location. He further states that some of this bronchial occlusion is permanent, causing reduction of functioning lung tissue. The extent of the reduction depends upon the duration of the disease and the severity and frequency of the attacks.

Cooke doubts the importance of bronchial or bronchiolar muscular hypertrophy or spasm. He feels that the most important factors in the production of asthmatic wheezing are edema of the bronchial walls and bronchial plugging with tough viscid exudate. He attributes the beneficial effect of adrenalin to its action in lessening edema rather than to any effect on smooth muscle and draws an analogy to the action of adrenalin in edema of the nasal mucosa and on the exudative processes of allergy of the skin.

Walzer likewise attributes major importance to mucosal edema and obstructive mucus. He suggests that the muscular hypertrophy may not be due so much to recurrent spasm as to the increased work necessary to overcome bronchiolar obstruction.

There appears no doubt that mucous plugs which may be retained for long periods, gradually becoming inspissated and causing local areas of atelectasis and emphysema through obstruction, plugs which are the original source of the well-known Curschmann's spirals, are often an important factor in the obstructive symptoms of asthma. Such plugs in the larger bronchi have been found on bronchoscopy and their removal in this procedure has relieved asthma. Lamson has described such a case in which the plugs had become canalized, the canals being in turn filled with tenacious mucus of more recent origin.

It seems probable that improvement after expectorants such as the iodides, iodized oil, ether in oil by rectum, and bronchoscopy, may be due in part at least to loosening and subsequent removal of bronchial plugs. On the other hand, not all even of the fatal cases of asthma show increased secretion of mucus or bronchial plugs, and it seems probable that both bronchospasm and bronchial obstruction play a part.

Emphysema.—A temporary emphysema is part of every asthmatic attack. Air accumulates in the lungs until the alveoli are distended and the whole chest is expanded. This condition clears up with the subsidence of the attack leaving no permanent changes. Continued asthma, mild but continuous, or intermittent and severe, may produce a true emphysema which is permanent and crippling. The temporary or "functional" emphysema is a part of the pathologic picture of asthmatic paroxysms. Emphysema with its tissue changes is a complication and a sequel to asthma.

Subcutaneous emphysema. Subcutaneous emphysema appears to be a rare complication of the acute asthmatic attack. Sheldon and Robinson (1936) found reports of 9 cases and added 1. Kirsner (1937) added an eleventh. There have been a few more recent reports. The condition occurs chiefly in children. All reported cases recovered in from 4 to 14 days. Faulkner and Wagner (1937) have, however, reported one case of fatal spontaneous pneumothorax with subcutaneous emphysema in an asthmatic. This was in a

59-year-old woman. There is no specific treatment. Alveolar rupture may occur either at the hilus or at the periphery, after which air migrates through the tissues, usually into the mediastinum and upwards to the neck, often involving the face also. Diagnosis is facilitated by the audible crepitation on digital pressure over the swollen area. This is best heard with the stethoscope applied to the region.

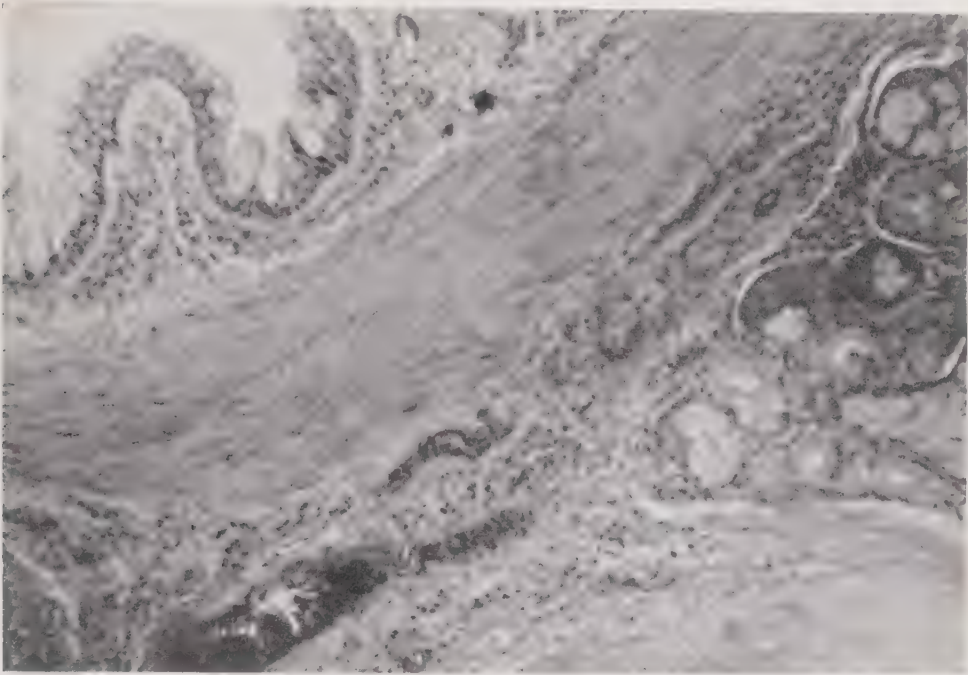


Fig. 300.—Pathology of asthma. Higher power, showing infolding of mucosa, moderate thickening of basement membrane, muscular thickening, and epithelial degenerative changes. Moderate cellular infiltration.

Heart.—That there may be cardiac manifestations associated with experimental anaphylaxis is indicated in the work of Criepp who found various arrhythmias, and auricular or ventricular asystole followed by cardiac standstill, during guinea pig anaphylactic shock. It cannot be definitely said that this is due to anaphylaxis since the same phenomenon is observed in asphyxiation.

Although Macdonald mentioned ventricular hypertrophy as very frequent, Kountz and Alexander, Michael and Rowe, and Vaughan found no cardiac enlargement in a number of cases. Lamson and Butt take exception to the statement of Old that the death rate from organic disease of the heart was three and one-fourth times greater than normal in persons dying with bronchial asthma, and to that of Dublin and Marks that the mortality is about two and one-third times normal. From a study of their series of fatal "asthma" Lamson and Butt question the implication that allergic asthma predisposes to cardiac disease. They attribute the presumed erroneous conclusions to erroneous reports of causes of death, and the impossibility of correcting the crude data.

Alexander has observed that during the asthmatic attack the heart often appears radioscopically smaller than normal, and suggests that, with bronchospasm, there may be diminished cardiac filling due to diminished intrathoracic negative pressure. He and his collaborators found in 15 necropsied cases, that

5 were complicated by superimposed diseases. Of the remaining 10, two showed right ventricular hypertrophy, two had right ventricular dilatation and 6 showed no pathologic changes in the heart.

The evidence strongly suggests that in the absence of complicating disease (including emphysema) the heart is not seriously damaged even in long-standing asthma. Hansen reported that in his 15 autopsied cases mentioned above, the 4 in which asthma was the cause of death showed normal hearts, except for 1 case in which there was slight hypertrophy and dilatation of the right heart.

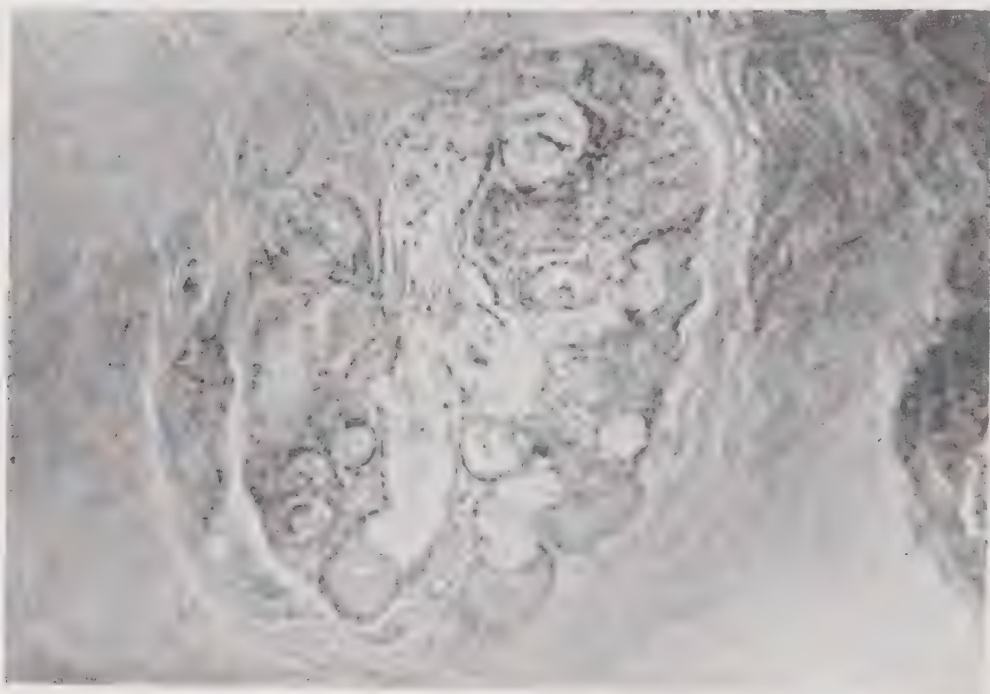


Fig. 301.—Pathology of asthma. Showing hypertrophy and degeneration of mucous gland.

but no evidence of failure. They seem to be the cases who die of asphyxia from mucous occlusion of the bronchial passages, and are free from infection. The larger group of 11, whose asthma eventuated in acute or chronic pulmonary infection, usually showed cardiac pathology. Seven of the 11 had cardiac symptoms, 6 congestive failure. Three had hypertrophy or dilatation of the right ventricle, 4 of both ventricles.

Prognosis

Life Insurance Company analyses by Old indicate the ratio of actual to expected deaths in asthmatics as 121 per cent .5 per cent; Dublin and Marks found the death rate 27.4 per cent in excess of the expected for men, somewhat higher for women. These deaths are often attributed to resultant cardiac disease. We have seen the hazard of drawing reliable conclusions from such analyses, due to the difficulty in determining the cause of death without autopsy, the frequently inaccurate use of the term asthma, and the fact that what appears clinically to be a cardiac death is not always such in fact.

Those who see large numbers of spasmodic asthmatics gain the impression that, although they may experience frequent periods of illness, their span of life is not materially shortened. Statistical analysis in allergic practice over

a period long enough to determine the final outcome might show otherwise. Even so there are at least two types of true asthma, for which the prognosis differs. We must return to a classification such as that originally elaborated by Willis and by Floyer, into the continuous form and the spasmodic or intermittent. The life span of the former may be distinctly shorter than that of the latter. Furthermore there is a special group which may be a subdivision of the former, the group of intractable asthmatics. Most deaths from asthma are in status asthmaticus.

Status asthmaticus. Clarke considers status asthmaticus a third form, basically different from the two just mentioned. It is characteristically a period of very intense dyspnea lasting several days to a week and with an associated outpouring of an extremely viscid tenacious mucous secretion which materially interferes with the lung capacity. Clarke has described massive pulmonary collapse.

Status asthmaticus terminates in any of four ways: (1) death, usually from exhaustion; (2) rapid termination with abundant expectoration after 24 hours or longer, (3) fever without localizing pulmonary signs, developing about the third day and lasting for three or four days, with disappearance of dyspnea prior to disappearance of fever; (4) pulmonary consolidation with physical findings of pneumonia. The fourth group usually recover and are free from asthma for a period thereafter.

Those who die without complications in an asthmatic attack appear to be rather a special group. As a rule their asthma has not existed for more than five years, although there is considerable variation. Lamson and Butt found deaths in all age groups, with the majority between ages 40 and 70. They found that approximately 40 per cent had the disease for less than five years, approximately 60 per cent for less than ten years.

We have mentioned the conclusion of Dublin and Marks that the life expectancy of asthmatics is not normal. Although Oliver Wendell Holmes described asthma as "the slight ailment that promotes longevity," and Bray says "many asthmatics pant on to a good old age," one must realize that asthma is a disease. It is a disease which may be fatal of itself and which predisposes to chronic pulmonary infection. Judging from the report of Hansen described above, the majority of asthmatic deaths are in those who have had these secondary infections and have developed secondary cardiac pathology. Life insurance mortality reports of the high incidence of cardiac pathology are therefore understandable.

Dublin and Marks found a higher mortality than they expected even in mild asthmatics, persons with but one attack a year of not more than two weeks' duration. They find that in all grades of severity the build is a vital factor. Both underweight and overweight asthmatics had excessive mortalities. They consider asthma a serious impairment as far as life insurance is concerned. They find persons with history of former asthma, but none within recent years, decidedly better risks and often acceptable for standard insurance.

Prognosis of immediate relief and future recurrences. As a rule the patient is not as interested in when he is going to die as when and how soon he will be relieved of his asthma. Statistical generalizations are difficult since so much depends upon the nature of the allergic excitant and upon the presence or absence of complicating infection. Obviously, results are usually excellent in pollen asthmatics and in other extrinsic asthmatics who can

successfully avoid the excitant. They are not as good among intrinsic allergies, especially those with respiratory infection. Unger's (1936) experience with 207 patients with all types of asthma followed for at least one year may be taken as representative of the experience of many. Twenty per cent were unimproved; 10 per cent of his series were dead but only 6 of the deaths were attributed to asthma. Some of these had been followed for as long as 13 years. Twenty-eight per cent of his extrinsic cases were cured, 52 per cent improved, as contrasted with 5 per cent intrinsics cured and 45 per cent improved.



Fig. 302.—Bronchial cast. Mucous plugs coughed up by an asthmatic. (Courtesy of Dr. Albert H. Rowe.)

The question arises as to when an asthmatic is considered cured. Rackemann (1928) reported 213 cures at the end of 2 years among 1,074 asthmatics, approximately 20 per cent. Four years later (1932) the percentage of the original number still free from asthma was reduced to 12 per cent.

We must conclude that although reasonable success often attends treatment of the acute episodes and may lead to a rather long interval of freedom, the asthmatic tendency is not cured but must be combated with each recrudescence. Of any group 85 or 90 per cent may still be having difficulty 6 years later. The above figures deal only with those patients who become entirely free from symptoms. Under appropriate supervision a much larger proportion continues improved, although not completely relieved. Cure should not be promised to the asthmatic but he may be given hope of a reasonable degree of relief for a much longer period.

Differential Diagnosis

Since all that wheezes is not asthma even though it be in the office of an allergist, and since good results depend in great measure upon the accuracy of diagnosis, it behooves the physician to establish his diagnosis thoroughly each time, using all indicated facilities.

Elicitation of rales.—In intervals between attacks, auscultation of the asthmatic chest may elicit no rales or wheezing. Such cases, seen for the first time, may raise some doubt as to the diagnosis. Fineman suggests that musical rales may be elicited in asthmatic children if the examiner will, with the child's chest at rest, compress it anteroposteriorly with the palm of one hand over the lower sternum, the other over the back. Clarke recommends for adults, that they blow air out of the lungs slowly against pressure, as in blowing bubbles through a tube in water or, better, using the spirometer as in vital capacity determination.



Fig. 303.—Pathology of asthma. Emphysema with rupture of alveolar sacs. This rupturing was so extensive that the left lung was little more than an air cyst.

The differentiation of various causes of periodic or continuous dyspnea can usually be made without great difficulty if a careful history is obtained and a careful investigation made. Patients may reach the allergist with a diagnosis of asthma who have, instead, cardiac decompensation, chronic bronchitis, emphysema, bronchiectasis, tuberculosis, pulmonary malignancy, enlarged tracheobronchial nodes, aneurysm, foreign bodies, laryngeal obstruction, sighing dyspnea, or other less frequent conditions. Roentgen examination, sputum examinations, blood counts, blood pressure readings, vital capacity determinations, circulation time, venous pressure readings, bronchoscopy, all may be of great assistance in selected cases. A careful, detailed history is indispensable and may be of more value than all other methods of investigation.

Roentgen findings. In an uncomplicated asthma there is seen peribronchial marking indicating thickening and little else. The heart shadow is normal. If seen in an attack there is emphysema and depression of the diaphragm. There may be the appearance of longitudinal folds especially on the right side of the diaphragm. This has been attributed to distortion and spasm of the diaphragm.

With complications the x-ray findings are characteristic of the complicating condition such as emphysema, bronchiectasis, cardiac enlargement, etc. Even in asthma of long standing and severe in character the findings in the film are those of the complicating conditions rather than the asthma itself.

Bronchiectasis.—This may occur as a complication of asthma or it may be seen by the allergist, because of a faulty diagnosis, in the complete absence of asthma. The history discloses a cough usually with abundant, foul sputum and dyspnea which is related entirely to exertion. Rest brings relief from the dyspnea and the patient may sleep through the night without attacks of dyspnea. If the condition has been present sufficiently long he may show signs of chronic infection. X-ray with iodized oil should verify the diagnosis.

Cardiac failure.—Asthma seldom develops in persons past 50 or 60 years of age who have no antecedent history of some other allergic manifestation. On the other hand, cardiac decompensation after these ages is common. Dyspnea developing after 60 years without history of other allergic condition and particularly in patients who state that their dyspnea has been present only a short time, on a statistical basis is probably cardiac in origin. A patient whose dyspnea has been present for months or even years is quite unlikely to be cardiac. The patients usually have a history of hypertension. Their description of their dyspnea is that of a "shortness of breath" rather than a wheezing dyspnea; it is definitely related to exertion except as they may have "cardiac starts" at night. Some of them may show râles which cannot be distinguished from those of true asthma. Some observers believe these are found in asthmatic patients who develop cardiac disease. These patients usually, but not invariably, show moist râles at the lung bases which may be present in the absence of dyspnea at the time of examination.

This condition may be found in young persons recovering from an infectious disease with resultant myocardial damage. Here the diagnosis may not be easy, but is most important.

It should be remembered that epinephrine and ephedrine may give the cardiac patient considerable relief. The relief is not as complete or satisfactory as in asthma but the patient may state that these drugs give him much relief.

Tuberculosis.—Tuberculous nodes may press upon the bronchi, and fibrosis and adhesions may also mechanically interfere with normal respiration. In advanced tuberculosis with cavitation there may be dyspnea which is not wheezing in character, is related to exertion, and relieved by rest. The patient may be able to sleep flat in bed and be undisturbed through the night. The cough is usually followed by mucopurulent or purulent sputum, and the sputum may be blood tinged or there may be frank hemorrhage. Sputum examinations and x-ray of the chest will be routine in these cases.

Emphysema.—Continuous or frequently recurring asthma may be followed by emphysema but true emphysema may occur in the absence of any history of asthma or other bronchial or pulmonary condition. These patients usually complain of the gradual development of breathlessness with little or no cough or sputum. The description is of "shortness of breath," is not usually accompanied by any wheezing and is related to exertion. These persons may be able to sleep flat in bed and are not awakened by cough nor dyspnea. They develop a barrel-shaped chest. Vital capacity determination may be helpful.

Malignant tumors may develop in the mediastinal nodes and press upon the bronchi or bronchogenic carcinoma may develop in the lung itself similarly pressing upon and even destroying the bronchi in the involved area. In these



Fig. 304.—Types of chest deformity associated with asthma.

First row: Flat chest with tendency to pigeon breast, seen especially frequently in the growing child. Generalized muscular asthenia is commonly present. Improvement in muscle tone, with graded exercises if necessary, often helps the general condition.

Second row: With beginning barrel chest, the clavicle becomes raised, appearing horizontal rather than dipping downward toward the sternum. Owing to the chest deformity and the allergic facies, depression of malar prominences, the first two figures of this row (not related) resemble each other to such an extent that they might be taken for brother and sister.

Third row: More pronounced emphysema with barrel chest and horizontal clavicles.

patients the dyspnea is usually gradual in onset, not paroxysmal, and usually is not accompanied by asthmatic râles. Hemorrhage is not infrequent particularly in the bronchogenic tumors. Physical signs may be limited to the lung involved. X-ray examination is quite dependable.

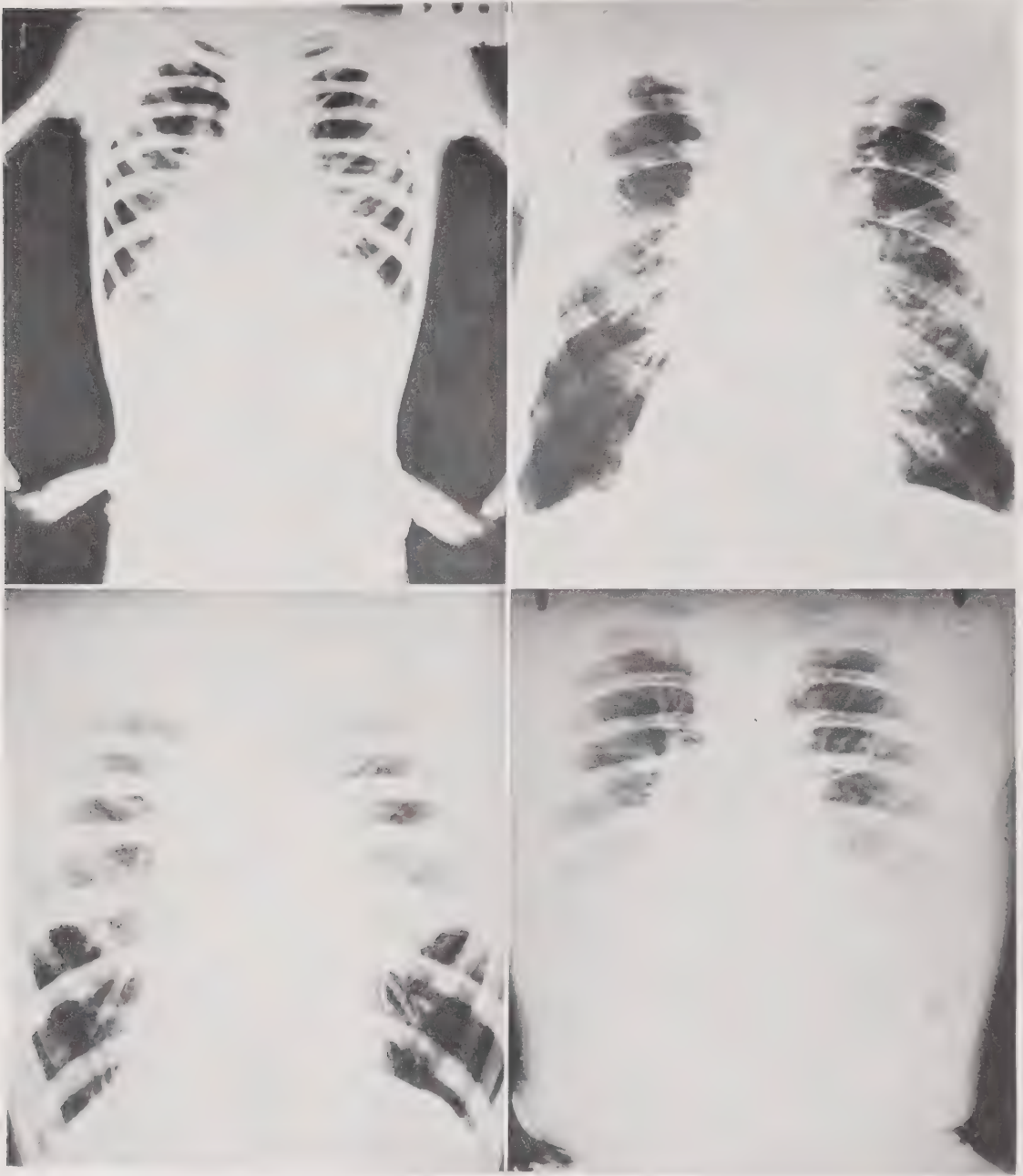


Fig. 305.—Types of roentgen findings. Upper left: increased hilus shadows with emphysema. Upper right: emphysema with some thickening of upper mediastinal shadow due to hilus shadows. Lower left: peribronchial thickening with increase in hilus shadows and bronchiectasis, especially in the left lower lobe. Lower right: increased bronchial arborization to left upper and both lower lobes. Increased shadow at bases is due to large breasts, not fluid. In all pictures, patient's left side is to reader's left.

Foreign bodies.—These are more frequently found in children but do occur in adults. The history usually indicates a sudden development of dyspnea and the patient, if adult, can usually date exactly the time and circumstances

of the onset of dyspnea. The dyspnea may be wheezing in character and there may be considerable cough often with mucopurulent or purulent sputum. The physical signs are usually, though not invariably, limited to the affected side. X-ray film should show the object if it is a metallic substance.

Sighing respiration.—This condition should occasion no trouble in diagnosis if the history is adequate and the patient's conduct watched during the consultation. The respiration is definitely sighing and is not a true dyspnea. It is not associated with cough or sputum, there is no wheezing, it is not related to exertion and it is not paroxysmal but continuous. It is due to emotional disturbance or conditions of stress and strain or a feeling of inadequacy. Physical examination and laboratory tests are entirely negative.

Emphysema.—Alexander stresses the importance of distinguishing types of pulmonary emphysema. Cases of nonobstructive senile emphysema, with associated bronchitis and consequent wheezing and cough, are often referred to allergy clinics for allergic study. It is important to distinguish these from the obstructive cases which usually occur at younger ages and are often associated with asthma. It is equally as important to recognize other sources of obstruction besides asthma.

Nonobstructive senile emphysema has been shown by Alexander to be due to skeletal changes, chiefly in the thoracic spine. Thinning of the intervertebral discs causes shortening of the spine; downward and forward pressure on the ribs; which are thereby rotated somewhat, so that their anterior ends are raised, the sternum is raised, and a barrel chest results. Senile kyphosis serves to further emphasize this nonobstructive or senile emphysema. Heckscher (1936) likewise ascribes some forms of nonobstructive emphysema to postural factors.

Prigal (1942) has called attention to a severe paroxysmal type of cough which seems to be definitely allergic with the site of the reaction in the larynx or trachea. It may be seasonal or perennial. It may be differentiated from asthma with severe cough by the entire absence of wheezing dyspnea and the negative chest findings.

There are other conditions which may cause disturbances in respiration and for a satisfactory list of these refer to Maytum's classification. They may be differentiated from asthma by careful investigation.

Nonallergic Treatment

In asthma as in nearly all of the clinical allergic manifestations, experience has shown that treatment based on concepts other than those of allergy often give material relief. Prior to the advent of allergy these were the only available procedures. Assuming that allergic therapy has been more successful than any of the others, one must yet realize that there is a sufficiently high proportion who are not relieved, and that a combination of allergic therapy with other nonspecific methods will sometimes accomplish the desired end. On the other hand, in this group of diseases possibly more than in any others, nostrums have flourished and new procedures, widely heralded at the beginning, have had great vogue for a time and then been forgotten. There is always a still newer one to take their place. It might be said that allergy itself was in this position at one time. But the fact that it has passed through the stage of trial and criticism and appears to be becoming an increasingly important phase of medicine removes it from the category. Since the allergic diseases are essen-

tially chronic and since even with allergic therapy there is usually some residuum of symptoms, many of its victims continue to chase the will-o'-the-wisp of promised cure. The physician should therefore be in a position to advise his patient as to the relative merits of the various nonallergic methods.

Sinus disease.—Except in chronic perennial asthma the incidence of sinus infection appears to be little if any more frequent in asthma than in other pulmonary diseases or indeed in the population at large. Kern and Donnelly find no higher incidence of sinus diseases in persons with uncomplicated hay fever or with seasonal hay fever and asthma than in the average run of the population. In perennial asthma there is a slightly higher incidence. They conclude from their studies that asthma complicating hay fever is, in most instances, due to allergy to pollens and other inhalant substances, rather than to the sinus disease. The slightly increased incidence of the latter is a secondary complication rather than a primary cause of the asthma.

In a study of 400 cases of sinus disease Bullen found that one-fourth presented evidence of chronic nontuberculous pulmonary disease such as asthma, chronic bronchitis and bronchiectasis. Only 12.25 per cent had asthma. In only 8.75 per cent of these did asthma begin at the same time as the sinusitis or later. Bullen interprets this as evidence against a strong etiologic factor. Ten per cent of the chronic sinusitis cases had chronic bronchitis and 7.75 per cent had bronchiectasis.

Weille concludes from his wide experience in the rhinologic treatment of asthma, that patients with either intrinsic or extrinsic asthma may be improved or cured even though retaining severe sinusitis, infected tonsils or abscessed teeth. A focus may exist in extrinsic asthma without positive relationship to the asthma save by making the patient's general condition worse. Occasionally cure may follow removal of an extrinsic allergen, while the patient ascribes his relief to some form of nasal treatment. Weille emphasizes the need for conservatism in the selection of patients and in the choice of operative procedure.

Sinus surgery.—The indications for sinus surgery in asthma are primarily the same as those for this procedure in conditions other than asthma. If the local pathology is sufficient per se to require treatment, such treatment may be given. The existence of bronchiectasis or of chronic bronchitis indicates the need for sinus study and for treatment if infection is found. The experience of those allergists and rhinologists who have collaborated in the study of asthma with sinus infection has very definitely been that allergic treatment should be undertaken first. If this fails to give relief, then sinus surgery will give added relief in a respectable proportion of these residual cases.

Weille found that 362 of 500 asthmatic patients had sinusitis. Sinusitis was slightly more frequent in the intrinsic than in the extrinsic group. Sinus operations on 100 of these included 17 intranasal antrum operations, 41 radical operations, 30 intranasal ethmoid, 5 external ethmoid, 17 sphenoid and external frontal procedures. Some improvement in the asthma was noted in 66 per cent, equally divided among the extrinsics and the intrinsics. More improvement was noted following conservative nasal surgery than after radical: 290 patients had no surgical treatment, being treated only medically, and the results were about the same.

Mullen reported on 216 sinus cases: 52 had had sinus surgery with no allergic studies and no relief. He feels that allergic study should precede sinus surgery.

Jacquelin and Chait described the results from intranasal surgery in 48 asthmatics with nasal obstruction and 26 with nasal infection, concluding that although a few improved, many showed no improvement and several be-

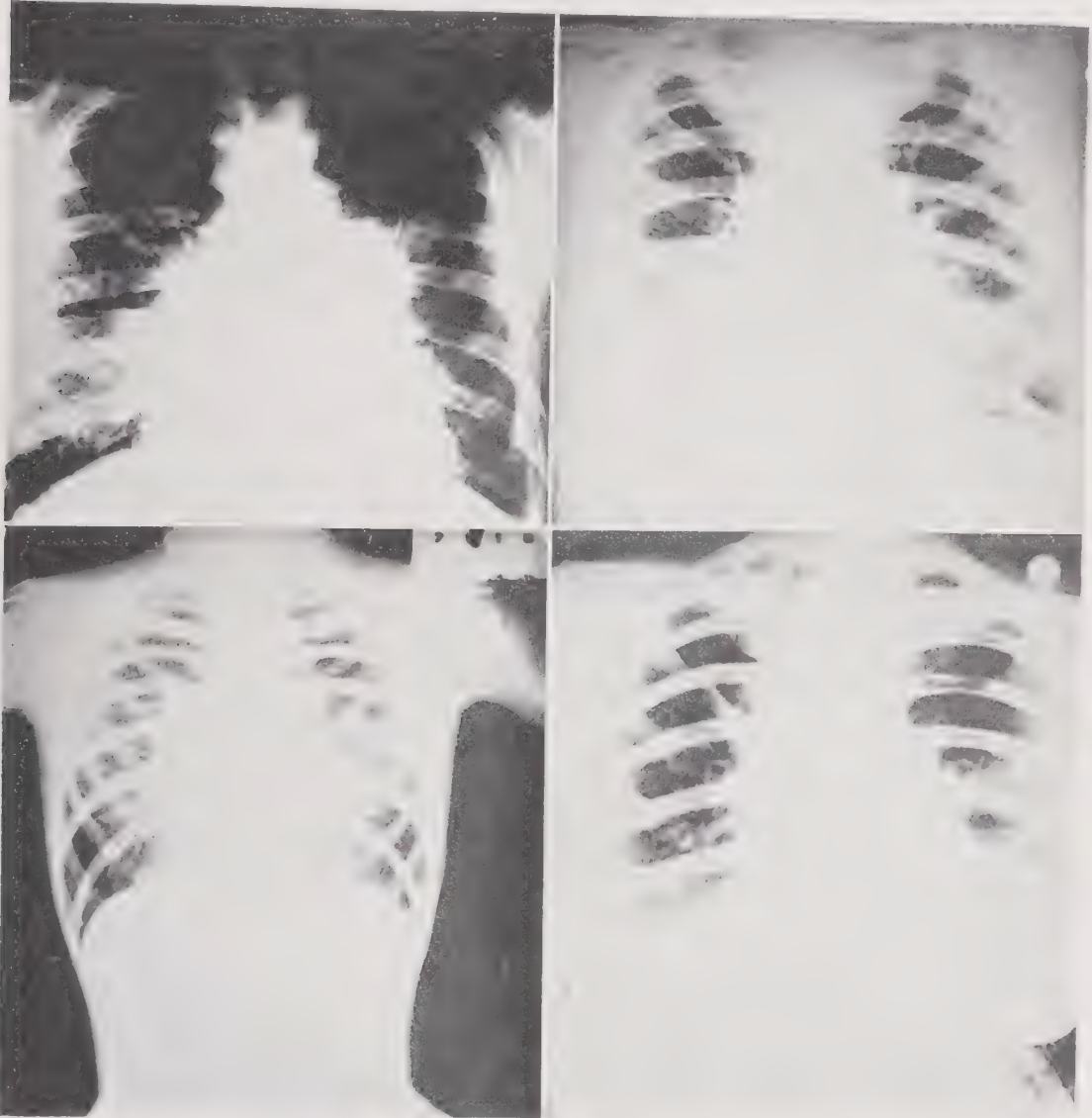


Fig. 306.—Importance of routine roentgen examination. All that wheezes in the allergist's reception room is not asthma. Upper left: malignancy. Upper right: dyspnea due to diminished air space (fluid). Lower left: child with an obscure metabolic disturbance involving deposition of calcium throughout the lung. Condition was progressive, not relieved by parathyroid therapy. Lower right: true asthma with associated advanced pulmonary tuberculosis and cavities, seen between sixth and seventh ribs. One should know whether one is dealing with true asthma and whether other pathology requires simultaneous treatment.

came worse. They feel that the presence of asthma is not of itself an indication for nasal surgery.

Warner and McGregor report that of 31 asthmatics treated by radical antrum operation and kept under observation for from 6 months to 2½ years, all were immediately relieved of the asthma. The relief varied from 2 weeks to a little over 2 years, with an average of 4 months. In only 2 did relief

persist more than 2½ years. Best results were obtained in those who had been asthmatic but a short time.

Schenck and Kern reported the results of radical sinus surgery in the form of the Caldwell-Luc operation in 35 asthmatics. The etiology of the asthma, whether extrinsic or intrinsic, appeared to play no part in determining results. They believe that this operation has certain advantages over intranasal operations and that the results are rather better, but even so the majority of cases relapsed after varying intervals. They feel therefore that this radical operation should be reserved for those cases of antrum infection which had failed to yield to other more conservative measures.



Fig. 307.—Bronchiectasis and iodized oil. In the early stages of bronchiectasis the picture is not clear-cut. In the lower lobes there are loose fluffy shadows of the affected bronchi and neighboring infiltrated lung.

Well-advanced bronchiectasis is characterized by excessive thickening of the lung markings along the larger bronchi, hilus gland enlargement, single or multiple areas of increased density surrounding the bronchi in the lung field. There may be considerable change in the picture immediately after abundant expectoration.

A radiopaque substance (lipiodol, lipiodine) introduced into the bronchial tree facilitates study of bronchiectasis. As a rule either of two pictures is observed. There may be multiple small abscesses in one or more lobes with bronchial dilatation or deformity, or there may be cylindrical dilatation of the bronchi with what appear like buds along their margins.

Figure shows multiple pockets and slight dilatation of a main bronchus in an asthmatic

One difficulty in reaching any decision as to the value of sinus surgery is that various rhinologists have used completely different surgical techniques. Ferris Smith, one of the first to employ complete exenteration of the sinuses, has reported better results than any other rhinologist in the treatment of

asthma. Recently Grove and Cooke have reported beneficial results from this type of radical surgery. Such an operation involves more than the radical Caldwell-Luc antrum operation, since it implies complete removal of the lining membrane of the antrum. Grove and Cooke found that 82 per cent of asthmatics with sinus infection were definitely improved following this operation, as contrasted with but 38 per cent following less extensive surgery.



Fig. 308.—Cylindrical bronchiectasis in left lower lobe with bronchi curving in whorls on the opposite side.

This dealt only with intrinsic or purely bacterial asthmatics. Among those with sinus infection and intensive reaction, 88 per cent were definitely improved following allergic therapy with the complete operation, while but 40 per cent were improved following the incomplete operation.

Results were not immediate, greatest improvement being observed after 6 months. At the end of 6 months the percentage of improved cases was 50. At the end of 3 years it was 75 per cent. The duration of the preexisting asthma appeared not to be a factor regulating relief except in those with associated lesions such as marked chronic bronchitis.

In discussing this paper Gay remarks on the frequency with which infecting organisms, particularly streptococci, may be found in the lining membrane of the sinuses even in the absence of frank purulent infection. In such cases their removal can be accomplished only by such a complete operation.

Disillusionments. In an article on disillusionments in nasal surgery W. W. Lewis summarizes, rather pessimistically, to be sure, the failure, from the viewpoint of the rhinologist, of more or less radical nasal surgery, especially in the presence of nasal allergy.

He points out that operations done for the purpose of increasing breathing space are usually made too extensively, so that after inflammatory reaction has subsided and scar tissue has formed, the resulting space may be many times larger than was originally intended. "In hypertrophic noses just one third of what appears mechanically necessary will prove sufficient as an end result, and it is far safer to undergo surgical resection, with a subsequent small additional resection, than to lose something which is entirely irretrievable." He believes that sinus surgery is tremendously overdone. If openings are made too large, reinfection is likely to occur with each attack of coryza. Radical exenteration with curettage of the mucosa is not good surgery in his opinion. He feels that a diseased mucous lining is preferable to exposed bone. Sinus surgery in children has been much overdone. Complete exenteration of the ethmoids is the quickest way of making a climatic invalid. He speaks of the maxillary antrum as by far the most assaulted sinus in surgery. The Caldwell-Luc operation is described as an extravagance in radicalism that should always have been challenged except in the presence of major pathology such as retained foreign bodies, dental cysts, tumor growth and the like. The danger of devitalizing neighboring teeth in this operation is stressed. There is also possibility of injury to the infraorbital nerve.

The above observations apply to rhinologic surgery in general, with no particular mention of allergy, and might be looked upon as the reminiscences of one who recalls all of his poor result cases while failing to remember his numerous good ones. Or, perhaps better, the rebellion of one who day after day sees in his office the pathetically unimproved results of other men, more radical and less competent than himself. In any event few will gainsay the essential truth of much that Lewis has said.

Coming to a discussion of nasal allergy he is even more emphatic. "In my opinion, of all the affections and conditions in the human organism where surgery has been not only the least beneficial but, in addition, largely harmful, allergic, vasomotor and hyperplastic affections of the nose have been the most outstanding. Especially and positively is this so where, in these conditions, radical operations upon the sinuses in addition have been done." He believes that conservative surgery sometimes has a definite place in nasal allergy but that major radical and destructive sacrifice of mucous surfaces and their underlying framework is rarely indicated. He prefers simple readjustment and correction of faultily placed nasal structures to extirpation, exenteration and resection. Submucous resection of the septum appears the best and most desirable method of increasing aeration when septal pathology is present, but even so Lewis has seen cases of vasomotor rhinitis initiated or exaggerated following this procedure. Such, however, are in the minority.

Grove (1947) insists that sinusitis is an important primary or secondary factor in the etiology of allergic manifestations. It may be the primary factor in infective asthma or it may be an important, though secondary factor, in true

sensitization asthma. He emphasizes the need of complete removal of diseased membranes. In 200 asthma patients with complete removal of the diseased membranes, 79.9 per cent were improved while the group in whom not all the sinuses infected were operated upon, only 35.2 per cent showed relief of their asthma. Those who had sensitization associated with their sinus infections showed a 16.4 per cent greater improvement in their asthma following the operative procedure. Best results were obtained when the asthma began after 21 years of age, had lasted less than five or not more than ten years, and when the operation was done at between 31 and 50 years of age.

Bronchoscopy.—This has been discussed under Diagnosis. Patients with chronic tracheobronchitis, bronchorrhea and definite suppuration of the lungs often respond well to bronchoscopic treatment. During the process cultures may be obtained for autogenous vaccine, presumably more reliable than those contaminated by the organisms of the upper respiratory tract. Occasionally a mucous plug may be found and removed. The importance of preliminary testing for cocaine allergy is obvious. A severe asthmatic who does not respond to other therapy should have the benefit of diagnostic and therapeutic bronchoscopy.

Waldrott states that bronchoscopy without an anesthetic can be done easily on the patient with intractable asthma and is of great value. He believes it should be used in every case of status asthmaticus which does not respond to the usual forms of treatment. Unquestionably, it is, at times, a lifesaving measure.

Iodized oil intratracheally.—Early enthusiastic reports on the use of iodized oil in the treatment of asthma and asthmatic bronchitis were made in 1932-1933 by Taylor, Fink, Anderson and by Cole and Harper. There have been four more recent reports. Good results have been estimated at from 56 per cent to 100 per cent.

Lipiodol is an iodized poppy seed oil containing 40 per cent iodine in organic combination. Lipoiodine, the ethyl ester of diiodobrassicic acid contains 41 per cent iodine. When injected intratracheally these radiopaque oils, which were originally used for x-ray diagnosis only, may be coughed up gradually, or absorbed, or may persist in the lungs for a considerable period. Iodism rarely occurs unless the oil is swallowed. Mineral oil is not used since it is a strong irritant, is not absorbed, and causes connective tissue proliferation.

Injections are given at weekly intervals or more frequently, depending upon the patient's response and fluoroscopic evidence of the amount of oil remaining in the lungs.

So far the only critical analysis is that of Crip and Hampsey who observed relief in only 3 of 20 cases of intractable asthma treated by intratracheal insufflation and in only 1 of 10 who received oil during bronchoscopy. They received 64 replies to questionnaires sent to allergists, otolaryngologists, and bronchoscopists, an analysis of which showed that in the experience of these 64, improvement in asthma and asthmatic bronchitis was observed in approximately one-fourth, with failure of improvement in three-fourths. Only one-third of the physicians who had tried this therapeutic procedure were still using it, and then only as an adjunct to medical and allergic management in well selected groups of asthmatics.

From their own experience, from the literature and from replies to the questionnaire, Crip and Hampsey list untoward reactions as follows: fever,

urticaria, arthritis, asthma, acute asphyxia, iodism, pneumonia, acute pulmonary collapse, caseation necrosis, fibrosis, massive consolidation, sudden circulatory failure with dyspnea and cyanosis, and immediate collapse with death within an hour. Hansen described a death a few minutes after a bronchoscopic examination with injection of lipiodol. Ikeda has described an oil aspiration pneumonia (lipid pneumonia) which, however, is more likely to follow aspiration of the heavier or more irritant oils.

Fuchs (1938) described spontaneous pneumothorax following the intratracheal administration of iodized oil. This may have been coincident or it might have been due to alveolar rupture from bronchial plugging with the oil, with increased pressure on coughing.



Fig. 309.—Cylindrical bronchiectasis, left lower lobe.

More recent experience and critical analysis have shown the method to be more dangerous than was originally supposed and several deaths have been reported. Complications have been fairly frequent and the favorable results claimed for the method have not stood the test of time. As a therapeutic measure the practice has been largely abandoned.

Roentgen ray therapy. The first report of relief of asthma following irradiation of the chest was that of Schilling who in 1906 observed this response as incidental to a diagnostic fluoroscopic examination. Others reported similar

coincidences such as following x-ray treatment of pruritus and acne, and deep therapy for carcinoma of the breast. In 1920 Drey and Lossen observed good results after roentgen treatment of the spleen in a case of leukemia with long standing asthma. Since then a number of investigators have reported success in the treatment of asthma following radiation of one or another portion of the chest, the spleen and various other organs of the body including thyroid, adrenals, liver and even the entire trunk. Good results from such helter-skelter treatment have led Walzer to suggest that the effect of treatment may be constitutional as well as local and may well be a form of nonspecific therapy.

A number of allergists have used this in refractory cases. Walzer reported good results in 2 of 20 such. Fred M. Hodges and I have treated 10, with good temporary results (two years) in one. A more recent report is that of Maytum and Leddy. Their first case treated in 1931 was completely relieved for some time. With each recurrence he has had similar periods of relief with roentgen therapy. In their total series of 23 patients, 22 per cent gained satisfactory relief lasting many months, 35 per cent obtained moderate relief for from three weeks to two months and the remainder received no more than 25 per cent relief, of short duration. They attribute good results to decrease in the secretory power of the mucous glands in the bronchi, liberation of antibodies by destruction of leukocytes, and possibly a stimulative effect on the production of eosinophiles. They treated the anterior mediastinal area, the paravertebral area and the splenic area, alone or in combination. Success and failure were obtained in each area. They favor irradiation of the mediastinum through the two paravertebral fields since it causes less gastrointestinal reaction. However, they state that possibly better results occurred when the anterior mediastinum was irradiated in addition to the paravertebral fields.

Patients usually responded with slight headache, lassitude and apathy, but rarely with nausea and vomiting. Some experienced pain over the back for one or two days and an occasional patient had slight exacerbation of his asthma. Improvement commenced within twenty-four hours or slightly longer.

Oxygen and helium.—Severe intractable asthmatics, especially when cyanosed, may obtain a measure of relief when placed in oxygen tents. Oxygen properly given by nasal catheter has occasionally in the writer's experience been almost life saving. On the other hand I have seen a near fatality in an oxygen tent in which the semiconscious patient, allergic among other things to feathers, was propped up with six feather pillows.

Barach has utilized the fact that helium is seven times lighter than nitrogen or oxygen. The patient is placed in a specially constructed tent into which a mixture of 25 per cent oxygen, 75 per cent helium is introduced. This has about one-third the weight of air and is therefore breathed three times as easily. Helium is an inert gas, exerting its beneficial effect only by virtue of facilitating respiration. It is best given with special apparatus, the ordinary oxygen tent being inapplicable.* Oxygen content of the gas mixture should be determined at frequent intervals, since helium is an inert gas and sufficient oxygen must be supplied.

*The simplest consists of a mouthpiece and mask and Douglas rebreathing bag. These and the special helium-oxygen tent may be obtained from the Oxygen Therapy Service Company, 201 E. 56th Street, New York, N. Y., or through the Linde Air Products Company which has branches in most large cities. The Benedict Helmet Respiration Apparatus is manufactured by Warren E. Collins, Huntington Avenue, Boston, Mass.

The pressure in the closed gas compartment should be slightly above atmospheric. During the asthmatic paroxysm there is an increased negative pressure in the chest which causes an accumulation of blood within the lungs and promotes the exudation of serum into the alveolar spaces with resultant edema. Positive pressure tends to counteract this congestive tendency in addition to facilitating inspiration. Some patients prefer a positive pressure of from 1 to 5 cm. water, others from 0.5 to 1 cm. This must be determined in each case. The special helium-oxygen tent contains a gauge by which this may be adjusted.



Fig. 310.—Same subject as in Fig. 309 with more oil, which brings out another dilated bronchus, higher up, which appears only as a shadow in preceding figure. (Oil roentgenograms, courtesy of Dr. Dean B. Cole, Richmond, Va.)

Barach recommends treatment periods of from 15 minutes to 1 hour. He does not suggest this as a substitute for adrenalin or other allergic treatment but as an adjuvant which primarily gives rest to a laboring patient.

Some degree of relief is obtained within a few minutes although it may be from two to eight hours before bronchospasm is relieved. In some instances as short a period as from two to five hours in the helium-oxygen tent suffices for relief from status asthmaticus. The patient becomes again responsive to adrenalin and needs no more helium treatment. In other cases periodic inhalations for from two to five days are required.

A most interesting observation is that adrenalin-fast patients become responsive to adrenalin after a period in the helium-oxygen tent. As was mentioned in the discussion of the adrenalin-fast patient, this suggests the possibility of a subconscious fear factor which may set up a vicious cycle responsible for the perpetuation of status asthmaticus.

Digitalis.—Digitalis should only be given when there is clear-cut evidence of circulatory failure. The writer has seen one death in an uncomplicated attack of status asthmaticus which he believes was directly due to digitalis. A woman had had intractable asthma for a number of weeks. Her physician, feeling that after this protracted period of respiratory difficulty her heart must be worn with the strain, prescribed digitalis. A few days later she died. At autopsy the heart showed no evidence of disease. There was no dilatation or hypertrophy of the right ventricle. Her heart was, however, distinctly smaller than normal.

Wearn has shown that the cardiac output of a dilated heart is reduced. Digitalis reduces the size of such an enlarged heart towards normal and increases cardiac output. Conversely digitalis reduces the size of a normal heart and when this occurs the cardiac output is reduced. A normal heart, digitalized, loses in circulatory efficiency. If a heart is enlarged or dilated, digitalis is indicated. If it is of normal size, digitalis is contraindicated. Digitalis should not be given to a patient taking calcium, and vice versa.

Miscellaneous measures. Artificial fever produced by diathermy and other measures, surgical section of the sympathetic or vagus nerves, alcohol injection of nerves, and a few other procedures have been suggested in recent years, but either the good results first reported have not been subsequently confirmed or the methods have not been used widely enough to justify final conclusion.

Drug therapy has been discussed in the section on pharmacology. On the whole, nonspecific protein therapy has been unsuccessful or has given only temporary relief. Tuberculin therapy and nonspecific vaccine therapy fall in this group.

Sokal (1942) reported the treatment of 22 asthmatic patients with pertussis vaccine. Previously Beaver had reported one and Rawlings four such patients, while Blotner observed three. The results were said to be excellent. The method has not been generally used, and the later reports are not encouraging.

Occasionally climatic changes are beneficial. When one moves to a new environment one should take care not to carry along a portion of his old environment (furniture, cosmetics, pets, etc.).

European spas.—Allergists are consulted from time to time concerning the spa treatment of asthma in Europe. This type of treatment is much more popular on the European Continent than in America. However, the regimen is often beneficial for a time at least and the change of locale provides a pleasant interlude for the chronic nonresponsive asthmatic.

The two French watering places most famous for the treatment of asthma are La Bourboule and Mont Dore, both in the Pyrenees.

La Bourboule is celebrated for the treatment of childhood asthma. Its waters are strongly radioactive and rich in arsenic. At Mont Dore, 9 kilometers away and at a higher altitude, specialization is in severe adult cases.

CHAPTER LXXIII

HAY FEVER AND ALLERGIC RHINITIS

Historical notes. The writer recommends that all who are interested in the history of hay fever read the excellent contribution on the subject by Thommen and the popular volume by Durham.

The story of Bostock's summer catarrh since its first description in 1819 has been briefly outlined in the introductory chapters. It is of interest to review the attitude of physicians toward hay fever at the turn of the century, just prior to the development of our present understanding. Blackley's work had been accepted and pollen was generally recognized as the cause, the mechanism being explained in the magic word, idiosyncrasy. There were some who believed that only pollens could cause hay fever. Even Blackley went to extremes to prove this point, explaining symptoms following exposure to animals, such as the rabbit, as due to the fact that the rabbit had recently been in the neighborhood of hay. He carried this to an extreme in attributing hay fever apparently due to cat hair, to mice exposed to hay and straw in the barn and subsequently eaten by the cat.

Opinion generally was that summer catarrh was a new disease at the time of Bostock. Dunbar (1907) wrote "hay fever is to be considered as a product of modern culture." Sticker (1902) went to great lengths to discredit the claims of other investigators that hay fever from flowers and other substances had been mentioned much earlier in the literature. He accepted no description prior to that of Heberden (1801) who had also been quoted by Bostock. And yet Sticker writes, "It is unintelligible how the name hay fever was all of a sudden so widespread in southern England in 1828 that Bostock assumed it as well known." Phoebus who also considered hay fever a new disease explained this as due to the sudden rise and notoriety of the name due to some unknown semipopular writing. A modern interpretation would be that the disease was already well known to the laity, being even attributed to hay, long before the medical profession took cognizance of it. This phenomenon has occurred before.

Antiquity.—The natural history of the disease being better understood today, we are more inclined to give credence to the earlier descriptions of isolated incidences of what would today be called nasal allergy. Thommen gives detailed quotations from nine earlier writers, all of whom describe the disease with reasonable clarity. The earliest are those of Botallus (1565) and of Van Helmont (1577-1644). There were seven other articles in the seventeenth century. It is interesting that in these nine records prior to 1700 all but one describe the nasal and conjunctival symptoms, sometimes with asthma, as due to roses, particularly the odor of roses. Van Helmont alone did not mention roses but described a form of asthma which occurred only during the summer. This is very much what one would anticipate. The rose is an excitant that is obvious and easily recognized. Even within our own recollection, goldenrod, easily identified, was incriminated rather than ragweed. These ancient cases probably were allergic to rose pollen as are a number of persons today.

John Mackenzie found that even in Galen's time there was a record of persons with idiosyncrasy to roses. Sticker, limiting himself to the original concept of Bostock's catarrh as being due to the pollen of grasses, took exception to the quotations from the earlier literature and marshalled a group of other earlier quotations to show by comparison how the earlier descriptions could not have been of true hay fever. Today, with our awareness that many excitants other than pollens may cause allergic reactions, these quotations of Sticker assume especial interest.

Marcellus Donatus (1586) described a boy whose lips became swollen and his face covered with red and black specks each time he ate eggs.

In the fourteenth century Jagello, King of Poland, according to Martinus Cromerus, had such a distaste for apples that he fled from their aroma as if it were the most fatal poison.

Riedlin wrote that the Duke of Schomberg (1693) "with many Germans of that day" could not bear the sight of a cat, not even the odor of a hidden one, without dyspnea and vertigo. He states that others of his time were similarly affected by the smell of mice and dogs.

Lusitanus (1563) described persons who suffered from the smell or eating of cheese as though it were a poison. He also described a friend, a Venetian, who suffered from "attacks similar to hay fever" at the mere sight of a rose.

Concluding his evidence in favor of a new disease, Sticker wrote, "The number affected with Bostock's catarrh is comparatively insignificant. From the discoverer's first communication to the time when Phoebus instituted his careful and extensive investigation as to occurrence of the disease—therefore, in almost half a century—there were, at most, 300 cases to be found in Europe. Since then the number of cases has increased, and so considerably that we must allow a rise in morbidity, and not ascribe it alone to greater carefulness on the part of physicians. Undoubtedly the number of so-called cases is today exaggerated, for a great portion of them in the literature of the last thirty years have nothing in common with Bostock's catarrhus aestivus. The origin of the disease is veiled in obscurity. There is not the slightest support for placing its occurrence before Heberden's time. If history can at all be trusted, the disease must have originated through the concurrence of unknown circumstances, about the middle of the eighteenth century, and from a gradual, slow growth and frequency it has become much more rapid."

Leaving the discussion of the antiquity of nasal allergy, and its possible increasing frequency, which today appears to be an actuality, it is surprising how much accurate knowledge there was of the disease at the turn of the century. This is epitomized in the following abstracts from writings of that time.

Georg Sticker in Nothnagel's Encyclopedia (1902). The disease strikes the Anglo-Saxon race by predilection. Dr. Abraham Jacobi saw no cases among his German patients in New York although it was frequent among his English clientele. Dr. Chaveau observed the same in the French colony of New York. The disease is twice as common in men as in women. It affects almost exclusively the best circles of society and may be termed an aristocratic disease. "Smith alone, of whom we have already said that he was unable to diagnosticate the disease, reports that poor people, too, suffer from the disease in public hospitals." City dwellers are more predisposed than those in the country. "A hereditary predisposition has been proved with marked frequency, considering how rare the disease is."

The existence of a constitutional anomaly or diathesis underlying the individual predisposition was recognized. Sticker lists other diseases in the diathesis as rheumatism, gout, diabetes, corpulency, migraine, furunculosis, bronchitis, asthma. A neuropathic tendency was recognized. Suggested causes, which Sticker accepted with reservations, were listed as follows.

Hay (Timothy)	Decoction of flaxseed
Meadow-grass	Ipecacuanha
Fodder-grass	Tea
Rye (Phoebus)	Street-dust
Ragweed	Bed-dust (Longueville)
Bean-blossoms (James Bird)	Heat (Bostock)
Roses	Cold (Smith)
Limes (A. Smith)	Bright light (sun, gas, petroleum; electric light is harmless—J. Bloom)
Cantharis	Ozone
Jasmine-blossoms	Vapor of burning sulfur
Mangifera (Gordon)	Emanations from hares, rabbits, calves, young pigs, cats (Wyman)
Nettles (Simpson)	Odor of roast hare (Thorowgood)
Seaweed (Gordon)	Frequenting concert-rooms, dance-halls, theaters, restaurants, or railroads (Hack)
Maize-blossoms (Deacke)	
Grain in general	
Rice (Cornaz)	
Peach-blossoms	

While giving Blackley due credit for his observations on pollens and criticizing some of his investigative procedures, Sticker concluded that in all probability it will be found that Bostock's summer catarrh is an infection. He mentioned Helmholtz' finding (1868) of a motile vibrio-like body in the nasal discharge. Also Farrar Patton's demonstration that

these vibrios resemble the foveilla particles from the interior of grass pollens so closely in size, form, color and arrangement, as to arouse doubt concerning their true nature. Even so, he felt that the dependence of the disease on season, its variation in time of onset in different countries, the character of the symptoms, and the correspondence in time to growth of insects, fungi, etc., also point strongly to an as yet undiscovered parasitic agent.

It is interesting, in view of the weight that we attached to the German scientific pronouncements of the period 1900-1915, as being most authoritative and representing the highest type of critical investigative effort, to review them after the lapse of a quarter century. The statements are still most positive. The only difficulty is that in the interim they have been proved erroneous.

E. Fletcher Ingals, in Twentieth Century Practice of Medicine (1896). William Daly of Pittsburgh (1882) first called attention to hyperesthetic areas of the nasal mucosa in the hay fever victim. Sajous one year later presented his theory of *Zones Hyperesthesiques* as responsible for hay fever. Many other rhinologists confirmed these reports, each as a rule having found a slightly different hyperesthetic zone.

Ingals wrote that heredity and the neurotic diathesis undoubtedly predispose to this infection while a great variety of agents may excite the attack. Among these he mentioned pollens but emphasizes throughout that three essential factors are necessary: the neurotic habit; local hyperesthesia; and the presence of irritating substances in the atmosphere. The experiment of John Mackenzie of Baltimore who caused a lady to have an attack from smelling a rose which unknown to her was artificial was quoted as evidence of the neurotic diathesis.

The major portion of Ingals's contribution consists of a description of methods of nasal cauterization. He quotes Roe as stating that a very large percentage of cases may be relieved or entirely cured by cauterization; and Sajous, that about 45 per cent may be cured and 25 per cent greatly relieved.

The vogue of nasal cauterization in this country is indicated by the statement of John Mackenzie at the American Medical Congress in 1895 that he was happy to find no mention made of the pollen theory in discussion of the causes of hay fever since this theory stood in the way of any proper comprehension of the disease.

Ingals described a case interesting from the modern angle, that of a patient who could eat tomatoes and watermelon with impunity except during the hay fever season, at which time they caused violent gastrointestinal disturbances.

J. Garel, in Le Rhume des Foins (1899). In the last year of the nineteenth century Garel contributed a very complete monograph in which he summarized prevailing theories as follows.

1. Meteorologic theory of Bostock (heat, light, dust, etc.).
2. Pollen theory of Elliotson, Morell Mackenzie and Blackley.
3. Microbic theory of Helmholtz.
4. Nasal theory of Daly.
5. Neuroarthritic theory, the theory of an allergic diathesis, favored by Gueneau de Mussy, Trousseau, Parrot and Desnos.

6. Eclectic theory, to which Garel subscribed, which adopted portions of each of the preceding except the microbial, postulating an hereditary or acquired nervous temperament, an unusual susceptibility or excitability of the nasal mucosa and the action of an external irritant. He emphasizes that treatment of any of these three factors may bring relief. This explains the good results reported with various methods. Garel described a surprising number of external excitants, from the experiences of his own patients, some of them agents which we have rediscovered twenty-five years later and whose importance has been proved by positive skin reactions. Most of these were in his series of nonseasonal allergic rhinitis, "*coryza aperiodique*." The excitants listed include:

Blossoms of fruit trees	Iris	Orris root
Change of temperature	Library dust	Orchid
Clothing	Lilac	Pepper powder
Coal smoke	Lycopodium	Pyrethrum
Corn husk	Mattress dust	Rice powder
Flaxseed	Odor of frying food	Soap powder
Heat	Odor of various perfumes	Sunlight
House dust	such as lavender, pepper-	Tobacco smoke
Humidity	mint, rosmarin	Tunnel smoke
Illuminating gas smoke	Cinchona powder	Varnish
Ipecac	Oil smoke	Wheat flour (in millers)
		Wheat (threshing machine)

He speaks of orris root as frequently causing coryza among coiffeurs. One source of difficulty which appears to have been a very real one at the time is no longer a factor. He describes a man who, each time he attended the opera, experienced coryza and asthma due to the large quantity of lycopodium in the air. Lycopodium was used on the stage to simulate rain storms and whenever a fire was called for.

W. P. Dunbar, in *Osler's Modern Medicine*, 1907. Here we reach the final theory proposed before the development of the allergic concept. Dunbar accepted the idea of (a) an individual predisposition and (b) a definite exciting agent. He commenced his study in 1895, first endeavoring to identify an infecting agent. Having convinced himself that none existed, he then turned to the study of pollen. Finding that spiculated pollen caused no trouble while smooth grass pollen did, he dismissed the idea of mechanical irritation as a dominant element. He next turned to a study of the rod-like bodies resembling bacteria which could be demonstrated inside the grass grains. He found them to be starch and inert on the nasal mucosa. During this study he extracted a chemical substance from the pollen which appeared to contain the active irritant. He found this to be an albumin.

"It was difficult to accept the view that a well characterized albumin represented the poison of hay fever. It appeared too new and startling that a chemically pure albumin, perfectly indifferent in its action to most persons, should be for certain individuals such an extraordinarily active poison. Even now no analogy presents itself to my knowledge." Further studies showed that this was not an enzyme and Dunbar concluded that it was a toxin, attached to the albumin, a toxalbumin.

The "toxalbumin" caused severe irritative reactions when applied to the mucous membranes of hay fever patients. Alarming symptoms followed attempts at subcutaneous injection. Using as subject his assistant, Dr. Carl Prausnitz who later became well known to allergists as the codveloper of the Prausnitz-Küstner technic, he observed a most alarming constitutional reaction. "The first manifestations appeared in ten minutes, and consisted of severe sneezing, with plentiful secretion from the nasal mucous membrane and considerable swelling of both nostrils. After thirty minutes a dry cough appeared, with a slight tenacious expectoration, and at the same time the face swelled and became very red and cyanotic. A marked injection of the conjunctivae developed and later chemosis. In both ears there was a feeling of tension; objectively, however, no change could be perceived in the tympanic membrane. One hour after the injection tormenting asthmatic disorders with audible stridor arose; an hour later an urticaria-like eruption of large wheals appeared over the whole skin, associated with violent itching; three hours after the injection the forearm began to swell. The edema spread during the following night to the whole arm. The edema of the arm and a turgid appearance of the face remained for several days. All other objective phenomena had disappeared by the next morning."

The experiment was repeated at a later time, when Dunbar believed he had neutralized the toxin with an antitoxin. "There were no phenomena at the site of injection, but the toxin was freed in the body. About one quarter of an hour after the injection itching of the nose and upper lip appeared, with sneezing, lachrymation and itching of the eyes, followed by weakening of the heart action almost to the point of complete cessation. Later asthmatic disturbances and urticaria appeared."

Dunbar next attempted to produce an antitoxin. He produced a serum which after standing for an hour in contact with toxin destroyed the irritant properties of the latter when applied to the nasal or conjunctival mucosa. Today we would explain this in terms of *in vitro* neutralization of reagin.

Dunbar's horse serum, presumably containing antitoxin, was applied in the nose both prophylactically and phylactically. He reported excellent results in 56 per cent of 1,240 patients, partial success in 31 per cent and no success in 13 per cent. Some developed an increase in symptoms after using pollantin for a time and the term "pollantin poisoning" appeared in the literature. Dunbar quite correctly maintained that this was due to the development of an idiosyncrasy to normal horse serum. He himself developed this idiosyncrasy after repeated nasal instillations.

Since there is no toxin in pollen, it is rather surprising that he observed such a relatively high percentage of excellent results. However he recommended, with the specific treatment, the usual precautions against exposure to pollen such as sleeping with windows closed, the avoidance of needless railroad journeys, etc. Furthermore the opinion of contemporary users of pollantin was that it was of value only in light and moderate cases, not in severe ones.

He explained the freedom of the majority from hay fever on the assumption that only certain persons are sensitive or hypersensitive to his toxin.

Discussion.—We see then that prior to the advent of anaphylaxis, the groundwork had already been done, extrinsic excitant causes had been recognized, hereditary predisposition had been established, and the conception of an individual idiosyncrasy had gained wide acceptance. Only an explanation of idiosyncrasy was still missing.

Pathology

Kountz and Alexander, and Hansel have pointed out the close similarity in the micropathology of nasal allergy and asthma. Hansel lists changes in the nose and sinuses as:

- (a) Thickening, hyperplasia and polypoid degeneration of the epithelium.
- (b) Eosinophilic infiltration of the tunica propria.
- (c) Edema, round cell infiltration and connective tissue proliferation.
- (d) Dilatation, compression and atrophy of glands.
- (e) Dilatation, thickening and compression of vessels.
- (f) Round cell and connective tissue proliferation in the periosteal layers.
- (g) Hyperplastic and rarifying or atrophic processes in the bone.

Changes (b) to (e) inclusive occur in the tunica propria. Eosinophilic infiltration is a prominent finding. The eosinophiles are so numerous that they escape into the nasal secretion. Changes in the sinus membrane are similar to those of the nasal mucosa.



Fig. 311.—Allergic facies. Flattening of malar prominence and tendency to breathe with mouth open, giving the appearance of "herring mouth."

Nasal mucosa. Grossly, the mucosa appears swollen, boggy, with pinkish gray discoloration due to epithelial hyperplasia. Continued edema may produce polypus formation. Polyps are more frequent and more pronounced over the anterior tips and lower margins of the middle turbinates and in the anterior ethmoid regions. It is here that maximal contact with the allergen takes place. Edema and polyposis may also occur in the sinuses, even completely filling the sinus. The antra and ethmoids are most frequently involved.

TABLE LXXIV.*—A SUMMARY OF THE ESSENTIAL CHANGES CHARACTERIZING THE HISTOPATHOLOGY IN ALLERGIC SINUSITIS AND HAY FEVER

1. Edema.
2. Hyperplasia and hypersecretory activity of the goblet cells.
3. Thickening and hyalinization of the basement membrane.
4. Eosinophilic infiltration.
5. Hypertrophy and hypersecretory activity of the mucous glands.
6. Presence of mucus in lumen of sinus and glands.

TABLE LXXV.*—HISTOPATHOLOGY OF THE VARIOUS STAGES OF ALLERGIC SINUSITIS

STAGE	MUCOUS GLANDS	EDEMA	GOBLET CELLS	BASEMENT MEMBRANE	AMOUNT OF MUCUS	EOSINO-PHILIA
Acute Stage	Hyperplasia Hypertrophy Hypersecretory activity	Moderate to marked	Hyperplasia Hypersecretory activity	Slightly thickened, granular or homogeneous	Moderate to marked	75-90 per cent
Chronic Stage	Hyperplasia Hypertrophy Hypersecretory activity and dilatation of glandular lumina	Moderate to marked	Hyperplasia Hypersecretory activity	Greatly thickened and homogeneous	Moderate to marked	35-90 per cent
Remission	Hyperplasia Little or no hypertrophy No secretory activity	Very slight	Not apparent	Moderately to greatly thickened and homogeneous	Little or none	15 per cent

TABLE LXXVI.*—SUMMARY OF THE ESSENTIAL HISTOPATHOLOGICAL CHARACTERISTICS OF ALLERGIC (ATOPIC) MUCOUS MEMBRANES OF THE ENTIRE RESPIRATORY TRACT AND ACCESSORY NASAL SINUSES

1. Hypertrophy and marked secretory activity of the mucous glands.
2. Presence of large amount of mucus in lumina.
3. Eosinophilia—from 15 to 90 per cent of all cells.
4. Edema of tissue.
5. Thickening and hyalinization of the basement membrane.
6. Hyperplasia of goblet cells with hypersecretory activity.

Polyyps. Polyp formation results from the loose structure of the stroma of the tunica propria. Marked local edema promotes prolapse of the mucous membrane, with a resultant pedunculated polyp. Polyyps are distended spaces filled with serum. Coalescence produces the cystic type of polyp, which may be unilocular or multilocular. Cellular elements are chiefly plasma cells, mononuclear, lymphoid cells and eosinophiles. The epithelium may be stratified columnar or stretched to a thin layer. Occasionally there is some fibrosis. The pedicle is usually rather dense connective tissue. Occasionally there are bony changes, especially in the region of the middle turbinate and ethmoid cells, and usually associated with polyp formation. These changes may be hyperplastic or atrophic, and are probably due to alterations in the blood supply. There is normally no caries, necrosis or ulceration.

Secondary infection may alter this picture, causing neutrophilic infiltration with connective tissue formation and eventually fibrosis. In this case bone involvement may lead to caries or necrosis. Superimposed bacterial infection is rather common especially in the sinuses, probably due to impaired movement of or absence of cilia.

*These summaries are by Steinberg, Bernhard, *Am. J. Clin. Path.* 4: 169, 1934.

Diagnosis

This usually presents no difficulty in pollinosis, when the season suggests the nature of the illness. On the other hand, many persons believe they have a cold when they are actually experiencing hay fever. This is especially true in the tree season. Many are unaware that pollinosis may occur so early in the year. Nonseasonal allergic coryza, whether intermittent or continuous, is often misdiagnosed by the patient and not infrequently by the physician. Often symptoms are so mild that there is little effort to seek relief. The writer has seen a number of cases, previously diagnosed simple postnasal catarrh, who were allergic to inhalants and foods, and relieved in great measure with appropriate allergic therapy. Others with apparently the same condition have not responded. However, if such a patient has failed to improve under other treatment, allergic study is justified.



Fig. 312.—Detail of flattening of malar prominence.

An etiologic allergen cannot be found in every case of vasomotor rhinitis. This may be because other factors can cause the symptoms or because one has not tested with the right allergen. According to Huber and Harsh 70 per cent of vasomotor rhinitis can be identified as allergic in origin. They believe that in the remainder endocrine dysfunction may be considered as an etiologic possibility.

Allergic facies.—Duke was, so far as I know, the first to emphasize the characteristic facial deformity in nasal allergy. This consists in an underdevelopment of the malar prominences, presumably due to underdevelopment of the sinuses. The result is a relatively flat looking face. The appearance is so characteristic that if one were looking at two brothers, one allergic and the other nonallergic, and a third boy not related, the two unrelated allergic children might resemble one another so much more that they would be judged the brothers. See Figs. 304 and 313.

Wasson made serial roentgenograms on children every four months from birth until the sinuses should be fully developed. He found that with chronic mucosal congestion, the various sinuses, except possibly the frontals, remain underdeveloped.

Bowen and Balyeat suggest that the so-called adenoid facies is often due to allergy. They speak of the over-riding upper incisors and the V-shaped palate, or "Gothic Arch." They found this type in 24 per cent of 100 children suffering from chronic nasal allergy and in but 5 per cent of 400 controls.

The writer finds depressed malar prominences more characteristic of chronic nasal allergy. Bowen and Balyeat might have carried the study a step farther, determining the incidence of allergic manifestations in children with adenoid facies.



Fig. 313.—Allergic facies. Two boys, unrelated, who, on account of facial configuration, might be taken for brothers.

The allergic salute.—The same writers describe two mannerisms quite characteristic of the allergic child with nasal involvement. The first is *nose-rubbing*, termed by Bowen, "the allergic salute." The child with nasal allergy often has a watery secretion which spreads in a film from turbinate to septum. Pressure inward and upward on the tip of the nose tends to widen the intra-nasal space, separating turbinates from septum and promoting aeration. The child with wet nose has discovered this and promotes aeration by passing the palm of his hand vertically along the tip of the nose while pressing inward toward the face. This is not wiping the nose. It is quite different from the transfacial flourish with the extended index finger seen in children whose only disability is that they have not received as much home supervision as they have deserved.



Fig. 314.—Allergic facies.

The second mannerism is that of "nose wrinkling." The child spreads the ala nasae slightly by drawing the upper lip to one side and upward. Sometimes this is bilateral. There is usually a simultaneous short sniffing inspiration. This accomplishes the same purpose and is distinguished from the ordinary sniffing of a child who is too lazy to blow his nose.

Significance of mucous polyps. Kern and Schenck believe that nasal mucous polyps are practically invariably allergic. They differentiate nasal polyps other than malignant into (1) mucous polyps or edematous fibromas; (2) mixed polypoid hyperplasia; and (3) papular hypertrophy, or mulberry polyp. It is the first that belongs in the allergic class. The mucous polyp is pale, smooth, translucent, white or gray or occasionally bright yellow tinged

TABLE LXXVII.—DIFFERENTIAL DIAGNOSIS OF ALLERGIC AND INFECTIOUS CONDITIONS OF THE UPPER RESPIRATORY TRACT IN CHILDREN*

History

Allergic

1. Attacks usually recurrent.
2. Often mild symptoms between attacks.
3. Definite relation to heredity.
4. Not contagious.
5. Not related to exposure to another case.
6. Constitutional symptoms slight.
7. Foods and inhaled substances often traced as causes.
8. Itching common.
9. Wheezing common.
10. Other allergic conditions present or in past history.

Infectious

1. Attacks usually single.
2. Usually clears up completely.
3. No relation to heredity.
4. Contagious.
5. Definite relation to exposure to another case.
6. Constitutional symptoms more marked.
7. No relation to foods or inhaled substances as cause.
8. No itching.
9. No wheezing.
10. Usually no other allergic condition present or in past history.

Examination

Allergic

1. Visible mucous membranes, pale, glistening, edematous.
2. Thin watery mucoid nasal discharge, mucoid sputum.
3. Smear shows eosinophiles 10 per cent or more.
4. Other signs of allergy often present.
5. Sinus involvement of hyperplastic type.
6. Wheezing breath sounds.
7. Roentgenogram shows bronchial markings increased.
8. Allergic skin reactions usually positive.

Infectious

1. Visible mucous membranes, hyperemic, red.
2. Mucopurulent or purulent nasal discharge and sputum.
3. Smear shows polymorphonuclear neutrophils as predominant cell; eosinophiles few or absent.
4. No other signs of allergy.
5. Sinus involvement of purulent type.
6. No wheezing breath sounds.
7. Bronchial markings not increased in roentgenogram.
8. Allergic skin reactions usually negative.

Treatment

Allergic

1. Epinephrine specific for symptoms.
2. Avoidance of specific allergens followed by relief.

Infectious

1. No relief from epinephrine.
2. Avoidance of food or inhalant substances produces no change.

Combined Allergic and Infectious

Primary allergic conditions are often secondarily infected. Cure depends on recognition and relief of the allergy. The body then overcomes the infection in most cases. This does not preclude treatment for the infection when indicated.

*Cohen and Rudolph, J. A. M. A. 97: 980, 1931.

with red. It is jelly-like and on inspection alone may be mistaken for mucus. These authors found that 30 per cent of bronchial asthmatics, 14 per cent of vasomotor rhinitis, 14 per cent of seasonal hay fever and 35 per cent of cases with hay fever and perennial asthma have mucous polyps. In contrast only 14 of 372 nonallergic controls presented this complication. These 14 presumably non-allergic cases were studied further. In 1 the supposed polyp proved to be carcinoma. Ten were found to have asthma, 1 asthma and vasomotor rhinitis and 1 vasomotor rhinitis alone. The fourteenth had a strong allergic family history and had himself had asthma many years before. He gave positive cutereactions to dust and feathers.

In a further study of over 2,500 patients they found 25 with mucous polyps who had not complained of an allergic condition. Of these there was only one with neither personal nor family allergic history nor positive skin reactions. In this case the polyp was found to be one of glandular hyperplasia, not a true mucous polyp.

The absence of eosinophiles in a nasal polyp does not rule out an allergic reaction. Kern and Schenck find that local eosinophilia of this type indicates an active response. The eosinophiles may be found in polyps during the reaction to hay fever but may disappear very promptly after the cause has ceased to act. Since differentiation of types is not always easy, all polyps removed should be subjected to microscopic examination. They consider it possible that bacterial allergy may play a part and that sensitization to bacteria may be a dominant factor. They note that mucous polyps occur especially in protracted and perennial cases. This suggests a bacterial factor. The role of bacteria is uncertain.

Roentgen Examination

The writer finds routine x-rays of the sinuses in all cases of allergic rhinitis and asthma to be a very helpful procedure. In the majority the evidence is confirmatory only, showing clear sinuses or some degree of cloudiness which may be due to thickening of the membrane, polyps or mucous secretion. Occasionally a dense shadow from empyema indicates the need for simultaneous rhinologic therapy. Such cases as a rule do not do well with purely allergic treatment, and it is incumbent upon the examiner to recognize such a state. Occasionally treatment of a frank sinus infection renders allergic therapy unnecessary. It prevents the embarrassment of a long period of desensitization without benefit, followed by quick relief after the patient has later visited an otolaryngologist. This may happen even though skin reactions have been clearly positive.

Polypoid changes are sometimes recognizable on films. They may be much more clearly delineated after the introduction of radiopaque substances such as lipiodol into the sinuses, as described by Proetz. However more detailed sinus study of this nature is not indicated until or unless the question of sinus surgery is raised by failure of relief following allergic therapy.

Properly exposed films of normal sinuses usually show them quite clearly demarcated. Slight general haziness usually indicates thickening of the lining membrane. In the frontal sinuses, this may be further confirmed by study of the septal markings which appear somewhat thickened and hazy. A shadow which completely obliterates the sinus usually indicates granulation, pus or tumor. As a rule one cannot differentiate the three. Occasionally a fluid level

may be visualized if the film is taken with the patient upright. The absence of a fluid level does not rule out pus. Erosion or invasion of adjacent bone structure suggests tumor. Absence of frontal sinuses must not be confused with infection. In the former case lateral plates will show that there is no room for a sinus at the base of the frontal bone. Polyps may at times be visualized in the frontal sinuses and antra as rounded areas of slightly increased density. The entire sinus usually appears somewhat hazy from thickened membrane. Very rarely a dense osteoma may be seen in one of the sinuses or in the orbit.

Transillumination of the sinuses does not give the same information as does the roentgenogram. The former is almost as reliable as the latter in diagnosing pus accumulations but may fail to show evidence of polyps or mucus since light may be transmitted through them. This point has been emphasized by Kern and Schenck.



Fig. 315.—Facies showing definite depression under eye.

Nonallergic Therapy

Air-conditioning.—Blackley constructed what was probably the first crude pollen filter, which was used with some success. Years ago it was observed that hay fever victims were relieved of their discomfort after entering the Caverns at Luray, Virginia. It was thought that the air was unusually pure or had some other curative effect on hay fever. An enterprising individual built a hotel above the caverns and ventilated it with air drawn up through a shaft from the cavern. This was to be the hay fever mecca. The building and ventilating system are still in use, but not as a pollinosis asylum.

In 1924 Van Leeuwen described an apparatus for removing allergens from the air. Atmospheric air was drawn into a chimney 115 feet high and passed through refrigerated pipes. Allergens were removed with the moisture which condensed on the pipes. The air was then passed into an allergen-free room. In 1925 Leopold and Leopold described an apparatus which forced air through a water spray, thus removing allergens. Later Cohen described a filter of woven wool and cotton through which air was passed. This was shown to be over 99 per cent efficient for pollens 10 or more microns in diameter. Peshkin and Beck (1930) described a simpler type of filter made of layers of cellulose, which could be fitted into any window. They introduced about 65,000,000 pollen grains into the filter. Not a single pollen was found on vaselined slides held over the outlet. None of these filters have been ideal. Patients have complained of noise, or in hot weather of the heat and stuffiness of the room. The filter pads must be changed frequently.



Fig. 316.—Allergic mannerisms. Illustrating nose wrinkling and "the allergic salute," both procedures designed to increase breathing space between the septum and turbinates.

The chief disadvantage of the ordinary filters which are fastened in window frames is that while they deliver pure and reasonably filtered air there is insufficient circulation in the room. As a consequence it becomes hot and muggy. Kahn improved the situation by stirring up the air in the room with a number of electric fans. Swineford developed a reasonably satisfactory cooling arrangement by blowing the fans onto a cake of ice. The increased humidity may be undesirable for those who respond unfavorably thereto.

Recently *air conditioners* have been installed in theaters, offices and homes. Gay (1933) found that hay fever patients were completely relieved within a few hours and pollen asthmatics within twelve hours, when remaining in a modern air-conditioned room.

Vaughan and Cooley (1933) found that in an ordinary room with an open window there was 23.4 per cent as much pollen as in the outside air. In an air-

conditioned room with windows and door closed the pollen count was 0.3 per cent of that for outside air. A patient with pollen hay fever found that in the air-conditioned room the degree of relief was about equal to that obtained with coseasonal pollen therapy. Relief persisted for three days after leaving the air-conditioned room even though the pollen concentration was relatively high during those three days.

While Vaughan and Cooley observed good results, Rappaport (1932) reported poor results in an air-conditioned room. The outstanding difference was that in the latter case filtered air from the outside was delivered into the room. The former observers found decreased humidity while the latter observed an increased humidity in the room. This was presumably due to the fact that moist, overheated air was continually being introduced. There appears to be a level of humidity above which some asthmatics do poorly.



Fig. 317.—One of the earliest air-conditioned buildings, at Luray, Va. It had been observed that persons with pollinosis were relieved when underground, in the Caverns of Luray. A house was built over the cavern and ventilated with air pumped therefrom.

Later Nelson, Rappaport and Welker (1933) studied cases in which humidity was also controlled, finding that sudden fall in barometric pressure might precipitate an attack during the season, even though the air was free from pollen and temperature and humidity were controlled. This may occur prior to a storm. However, this is a consideration quite aside from that of the value of air conditioning.

Mechanical filters require large fans and are noisy. The modern commercial air-conditioner with cooling unit is still too expensive for routine use. Crip and Green (1936) have described an electrostatic cleaner which removes dust by generating electrons in a high electrostatic field. The electrons tend to attach themselves to particles, giving them a negative electrical charge. In the electrostatic field these charged dust particles are attached to the positively charged surface of a series of plates. When the particles touch the plate the electrical force disappears and the particles are held by adhesion. This electrostatic device supplies and cleans 27,000 cubic feet of air an hour,

drawing it as desired from the outside or from the room. Only a small fan is needed, so that noise is reduced to a minimum. There are no filters to be replaced and cleaning is usually necessary only once each season. They find that this air cleaner removed one hundred per cent of pollen from the air and practically one hundred per cent of fine dust particles, including chemicals in liquid or solid form. Vapors and gases are not removed. The cleaner is said to be more efficient than the mechanical filter and has the advantage that it requires no replacement parts. It does not influence the temperature or humidity.

Discussion.—If one is unable to go to an environment in which the air is free from pollen, it is logical to attempt to remove pollen from the air of his normal environment. The simple expedient of keeping a room closed day and night is sometimes fairly effective. Vaughan and Cooley exposed slides simultaneously (a) outdoors; (b) in a non-air-conditioned room with no special precautions regarding doors and windows and (c) in an air-conditioned room. The total pollen deposit per unit area on slides during the ten days of observation was 6,303 for the first group, 1,476 for the second and 6 for the third.

Some are sufficiently relieved by spending the night in a pollen-free atmosphere that they tolerate exposure outdoors during the day, reasonably well. Others must spend more or even all of their time in protected rooms.

Nasal Ionization—Iontophoresis

This method of treatment popularized a few years ago did not give more than temporary relief to patients and has been abandoned. Neither rhinologists nor allergists are advising it. Those who were most enthusiastic about it have lost their enthusiasm and it is no longer even a topic of discussion.

Roentgen and Radium Therapy

Radium has been used for the local shrinkage of polyps. It does so by scar tissue formation. It has also been used in allergic coryza without polyp formation. Hansel, who has reviewed the literature, concludes that although the local application of radium is followed by relief of symptoms in more than 50 per cent, the method should be used only in those cases in which allergic methods have failed.

With improvement in x-ray technic this is also being tried in sinus infections and nasal allergy. Hatchette reported satisfactory results in 12 of 16 hay fever cases; no relief in 3 asthmatics. This method has not received sufficiently extensive trial to justify conclusions.

Nasal Surgery

The principles presented in the discussion of asthma apply equally in hay fever and allergic rhinitis. 1. In general, allergic therapy should be tried first even in the presence of obvious sinus infection. 2. Sinus infection should be treated locally, with or without surgery, on its own merits, in the same way that a similar infection should be treated in a nonallergic individual.

Obstructive processes are better removed. This sometimes entails submucous resection and, more often, removal of polyps. After long-continued allergic therapy polyps sometimes disappear, but relief is more rapid and

therefore more satisfying after removal. Tonsillectomy usually has no effect in relieving nasal allergy or asthma although occasional benefit has been reported.

Since upwards of 10 per cent of patients with pollinosis date the onset of their symptoms from an operation on the nose or throat (Huber, 1930), it is a safe precaution not to undertake surgery during the pollen season. If it is done it would be well to first test the patient's skin and ocular conjunctiva for possible sensitization to the pollen in season, even if he has had no symptoms. This naturally applies to those who are otherwise allergic or who have strong allergic family history.

Fenton has discussed nasal allergy from the viewpoint of the rhinologist. He remarks:

"Obviously no type of local treatment, whether medicinal or surgical, will do more than afford transitory relief for such people. Adrenalin is a life-saver for the severe case. Ephedrine, helpful at first, becomes an irritant if overused. Surgery should be limited to the restoration of proper calibre to the nasal passages by thinning down septal deflections; the turbinates should not be slashed out; and, unless bacterial allergy be due to gross infestation of the depth of sinus membranes, the sinuses should merely receive proper aeration and drainage rather than radical measures.

"Until a sinus has had the benefit of several weeks' conservative local treatment and careful study to eliminate any possible allergic factor, radical surgery should not be considered.

"Thickening of membranes seen in the radiograph is never sufficient evidence to justify radical operation; clinical signs must be present, and the swelling may be allergic."

Need for collaboration between rhinologists and allergists.—One afternoon the Havana Special was nearing Savannah, Georgia. On it were three physicians. The train had been blocked and was proceeding slowly. As the three gazed meditatively at the landscape, which for several miles had been monotonously unchanging, one remarked, "This ought to be great hunting country. I'd like to come down here some time with a couple of good bird dogs." The second replied, "I was just looking at all the ragweed along the tracks. Savannah should be a good place for an allergist to settle in." Whereupon the third, coming out of a semitrance, turned his gaze from the window to the two men opposite him, remarking, "Isn't that a perfectly gorgeous sunset?" All had been looking at precisely the same thing, but to each the dominant figure in the picture was different. The variation was in the points of view, major interests, or shall I say, in the coloring of the glasses.

The rhinologist and the allergist both look into the same noses, but too often they don't seem to be able to agree as to what they find there. Each has maintained that his own interpretation of the picture was the authentic one. Sometimes one has been right, sometimes the other, but neither has been correct all the time.

With the ancient Greek physicians there were two schools of belief, that of Cos and the school of Cnidus. So also until recently there were two schools regarding the subject under consideration, schools which disagreed, sometimes bitterly. But history again repeats itself inasmuch as each now begins to recognize the good points of the other and is willing to accept them, even to adopt them. Indeed, certain ones of both groups have found that the principle of the old stereopticon is best, that truest perspective of the picture is attained by fusion of the images observed from both points of view.

Both the rhinologist and allergist are now working much more in collaboration than formerly. The findings reviewed in this chapter indicate clearly that there is ample opportunity for coordinated effort which will result advantageously for the patient.

What proportion of office patients consulting the rhinologist are primarily allergic or have an allergic background? The few surveys reported are illuminating. Baum has found that among 2,000 routine office cases 10 per cent had allergy referable to the nose and throat and among 700 with primary nasal complaints 27.3 per cent were allergic. Hansel reports that in an analysis of 1,000 routine office cases there were 324 with nasal complaints. Of the latter, 44 per cent had nasal allergy. Roughly, from 25 per cent to 45 per cent of routine cases with primary nasal complaints exhibit an allergic factor. I think we can all agree that the vast majority of cases of vasomotor rhinitis first consult the nose and throat men. Huber and Harsch found 70 per cent of vasomotor rhinitis to be allergic in origin.

Kuhn* reviewed 3,657 consecutive cases in his eye, ear, nose and throat practice. Sixteen per cent came because of throat complaint, 20 per cent on account of nasal symptoms; 19.4 per cent of 720 nasal cases had primary nasal allergy. Of the allergic nasal cases 40.7 per cent were sensitized to inhalants, 5 per cent to foods, and 54.3 per cent to foods, inhalants and contact substances. Forty-seven per cent were satisfactorily relieved by allergic management alone; 27 per cent with allergic treatment plus conservative local nasal therapy; 21.7 per cent by allergic therapy plus nasal surgery. In the series there were only 3.5 per cent failures. This is a convincing example of the value of combined treatment.

*Kuhn, Hugh S. Personal communication, 1935.

CHAPTER LXXIV

MIGRAINE

Historical notes.—Undoubtedly the symptom complex which we know today as migraine is a phenomenon of remote antiquity. Possibly the trephining not infrequently observed in prehistoric skulls was performed at times for relief of this type of headache. We cannot be certain of this, however, since it was not until the first century of the Christian era that we find any record of serious attempts to distinguish this type of headache from the general group.

According to Balyeat, Aretaeus, toward the close of the first century, described a particular type of headache, paroxysmal in character, onesided, associated with nausea, and of more or less regular recurrence. He gave this type of headache the name heterocrania. Galen spoke of hemicrania although it is not certain that he was describing the same type of headache. The term migraine first appeared in the English medical literature in 1777. Modern recognition of the disease as an independent symptom complex dates from 1784 when Tissot described the condition in detail in his *Dictionnaire de Médecine*.

Explanatory theories of headaches probably date back nearly as far as man's personal experience with the malady. And through the centuries, the suggested etiologic factors have been indeed numerous. However, it is interesting that even at an early date some gastrointestinal association was recognized. This undoubtedly was due to the frequent occurrence of nausea and vomiting. Thus, Galen believed that headache was a result of irritation of the brain by black bile. Serapion in the eleventh century postulated a primary gastrointestinal etiology, with the transportation of hot or cold effluvia from the intestines to the head.

As early as 1850 clinical investigators commenced to suspect a relationship between migraine and what we now term the allergic diseases. The great French clinician, Trousseau, 85 years ago, described migraine as a part of the so-called asthmatic diathesis, which included such other conditions as urticaria, eczema, hay fever and some forms of hemorrhoids (pruritus ani?). By this I do not mean that at that time a basic etiologic similarity or identity was suspected in the common denominator of these diverse diseases which today we term allergy. The only point made at that time was that these diverse diseases occurred frequently in the same individual or the same families and that sometimes there was evidence suggesting an hereditary factor. The clear conception of these early writers, however, has since been confirmed by the more recent developments in the field of allergy, developments which have demonstrated the possibility of a common fundamental basis for such apparently heterogeneous diseases. Indeed, today it seems probable that even gout in some of its forms has an allergic linkage. Even though this disease is admittedly a feature of disturbed uric acid metabolism and manifests itself by certain pathologic changes which are certainly not characteristic of the other allergic diseases, yet the fact remains that persons who experience gout from one type of wine find that they drink other types with freedom from symptoms. The possibility, of course, exists that these cases of so-called gout may actually be cases of arthritis.

Lyman wrote, in 1895, that gout and headache have something in common, especially the headaches which resemble hemicrania and occur with the catamenia. He also remarked on the frequent association of migraine and hay asthma with gout, or their occurrence in individuals who later developed gout.

It was but natural that with an understanding of uric acid metabolism and its disorders in gout, a uric acid diathesis would be proposed explanatory of migraine. Lyman's treatment of this symptom consisted in the administration of mercurial cathartics, antipyrine, caffeine and alkali. He remarked that a glass of wine and a good dinner often relieve the headache because these drive the uric acid from the blood into the tissues.

Although there had been isolated opinions suggesting that food idiosyncrasy might play an etiologic role, such as that expressed by Brunton in 1885 who believed that milk and eggs might be responsible in certain cases, the turn of the century found research on the cause of migraine directed along quite a different line. This was the day of ptomaines and leukomines and at that time it was widely believed that the cause of migraine had

at last been discovered in paraxanthine, one of the leukomaines which had been demonstrated by Rachford and Wilson as being present in the urine of persons with migraine. Migraine was then considered to be an explosive neurosis caused by the presence of an autogenous toxin (leukomaine) in the blood.

The last thirty-odd years have brought an increasing realization that migraine is but a symptom which may arise as a result of the presence of any of several activating factors. Although I believe that allergy is responsible for the majority of cases, either as a predisposing or activating factor, I do not insist that allergy is responsible for all migraine. Indeed, in those cases in which there is a regular periodicity, especially a periodicity with the catamenia, it seems probable that the fundamental underlying factor is more likely associated with endocrine disturbance. Furthermore, there may be an associated endocrine factor in cases manifesting, at the same time, an allergic factor. Englebach found that among 370 cases with thyroid dysfunction 137 complained of headache. Among these 137 the headache was typically migrainous in character in 26. Among 257 headaches associated with pituitarism 46 were migrainous. Among 75 with thyropituitary dysfunction and associated headache, 21 were typically migrainous. Among 222 gonadal cases with headache, 57 presented the symptomatology of migraine. He observed that headache accompanied the catamenia predominantly in the gonadal and pituitary types of endocrine dyscrasia.

It is of special interest that allergic therapy in migraine has been more unsuccessful in those cases in which the headaches accompany the catamenia than in other types. The presence of an associated endocrine factor or a primary endocrine factor in these cases must be considered and should be taken into consideration in therapy.

So far as the writer has been able to determine, Lesné and Richet, Jr. (1913), were the first to suggest that migraine might be allergic. Rohrer (1915) suggested that the symptoms of migraine were similar in certain respects to those of anaphylactic shock. He stressed the fact that anaphylaxis was inherited only through the mother and that there is a high incidence of maternal inheritance in migraine. Pagniez and his associates (1919) again suggested the possibility of an allergic etiology in migraine and followed this by the report of a series of cases treated with peptone as a so-called nonspecific desensitizer. Joseph L. Miller was the first in this country to attempt peptone treatment of migraine, reporting benefit therefrom. Vaughan first demonstrated conclusively an allergic etiology (1927), by (a) the finding of positive skin reactions; (b) relief of symptoms following avoidance of foods reacting positively, and (c) subsequent induction of symptoms by the feeding of those foods which had reacted positively.

Pathology

The pathology of migraine is unknown. The attacks have been attributed to vasomotor changes of the meningeal vessels, particularly the middle meningeal artery. The supposed absence of vasomotor fibers in the cerebral vessels eliminated consideration of vascular changes within this organ. The recent report by Cobb of vasomotor control of the cerebral arteries reintroduces this possibility.

Goltman studied a patient who had been operated upon for supposed brain tumor, in whom changes in intracranial pressure could be followed by observation of the trephined area. In the prodromal period the face was pale, blanched, and the trephined area appeared sunken. With onset of migraine the depressed area gradually filled up, finally bulged. As the condition became more pronounced the facial pallor gave way to a flushed appearance, and vomiting occurred. Return to normal occurred after from twelve to seventy-two hours, the protrusion becoming again a depression. The patient was having a typical headache at the time of operation. The brain was found edematous, the vessels dilated.

Goltman's interpretation is that there is an initial vasomotor spasm with blanching of the face and depression in the skull. This is the period in which aura occur, numbness, tingling, ocular symptoms, etc. Vascular spasm produces ischemia of the brain or parts of the brain. The secondary stage is one

of vascular dilatation with resulting cerebral edema and consequent temporary disproportion between the size of the cranial cavity and its contents. Goltman believes that during this period there is temporary hypersecretion of cerebrospinal fluid with simultaneous hyperabsorption through the arachnoidal villi. The local pathology might be likened to an angioneurotic edema of a portion of the brain. Foster Kennedy (1933) believes that migraine is a symptom of focal brain edema and has described a number of cerebral symptoms which he believes are attributable to angioneurotic edema. These include migraine, epilepsy, evanescent neuritic pains and palsies, transient blindness, deafness, aphonia and hemiplegia. Temple Fay has shown that tension on the cerebral vessels will produce pain. This tension may be applied either in the direction of stretching longitudinally or circumferentially.

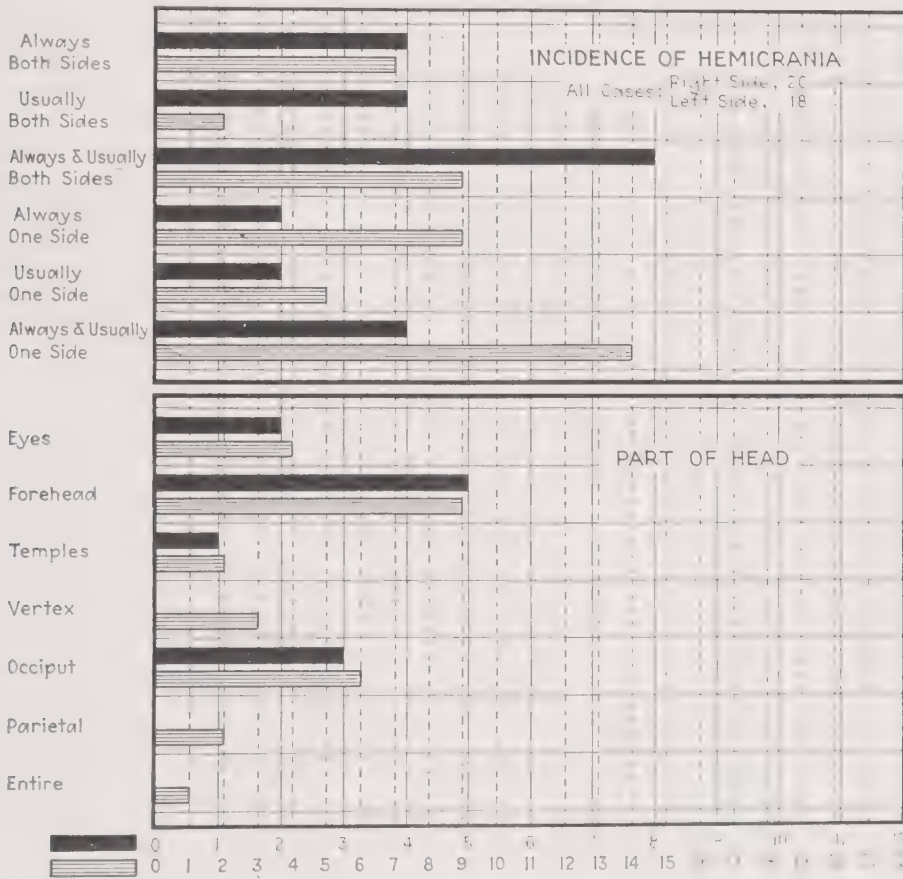


Fig. 318.—Migraine. In Figs. 323 to 327, black columns represent "poor results" in a series of twelve cases; while broken columns represent "good results" among twenty-two cases. Comparative lengths of columns may be interpreted as relative percentages. In the above, predominantly unilateral headaches respond better to allergic therapy than bilateral headaches. Location in the cranium appears not to be a factor.

Graham and Wolff (1937) and Wolff (1938) concluded that the headache is closely related to the pulsations of the temporal and occipital arteries, and that the intensity of the headache was correlated to the amplitude of the pulsations. Ergotamine probably relieves pain by contracting the smooth muscle in the vessel wall and reducing thereby the amplitude of oscillation of the vessel. When the pain is localized over certain vessels, compression of the artery, periarterial injection of a local anesthetic, or ligation, all will give relief. Torda

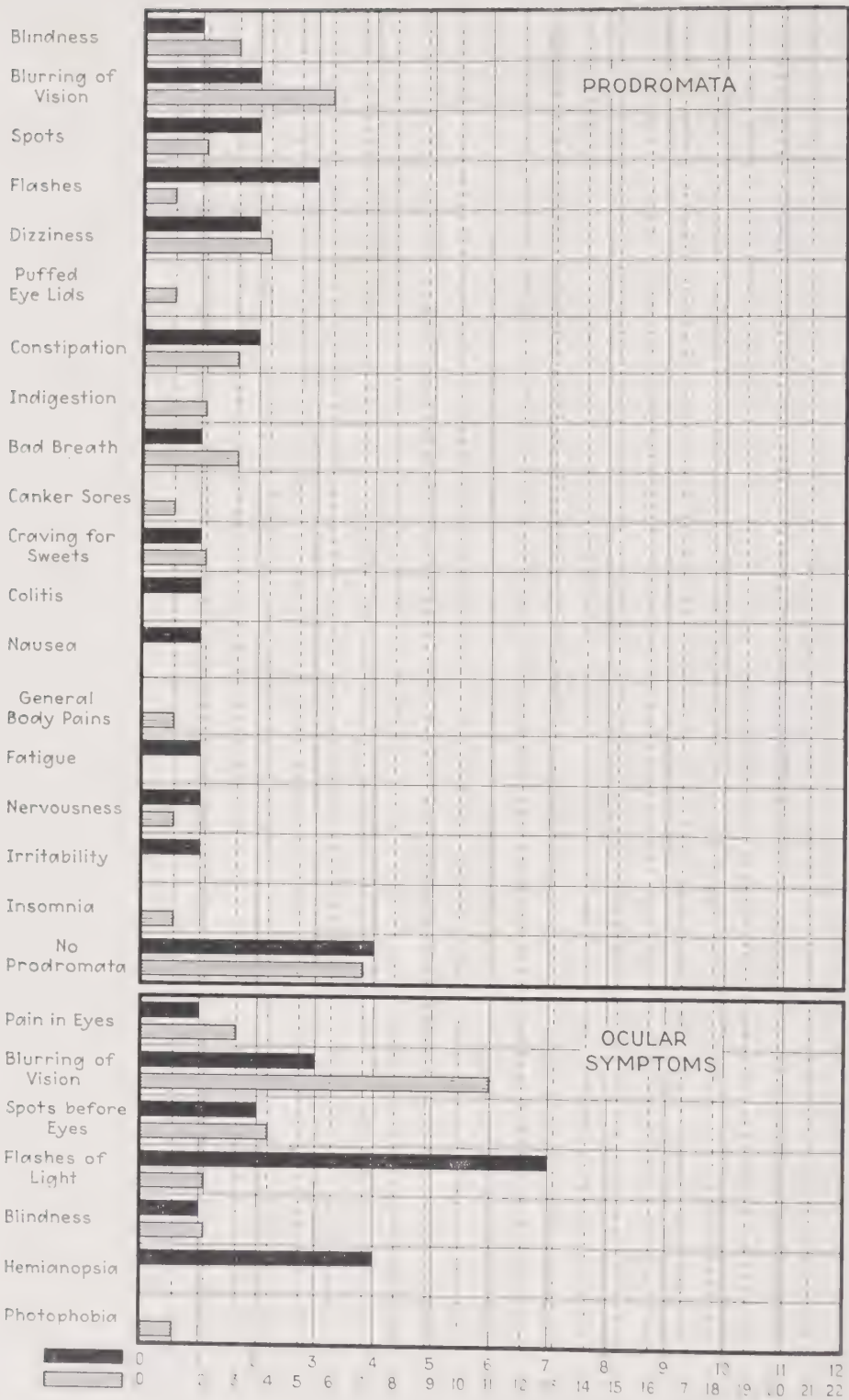


Fig. 319.—Migraine. Prodromata and ocular symptoms appear of little significance in pre-determining good or poor results from allergic therapy. If anything, a history of scotomata or hemianopsia presages poorer results.

and Wolff have shown that in animals increased dilation and oscillation induced by mechohyl will produce an edema of the vessel wall which they believe is the explanation for some vascular headaches with continuous steady pain.

Von Storch and Merritt found no significant abnormality or deviation from normal cerebrospinal fluid pressure in 44 cases with migraine. The protein content, cytology and serology of the fluids were normal.

It seems probable that further studies with ergotamine tartrate may lead to a more accurate understanding of the pathology of migraine. Lennox and Leonhardt find that ergotamine like epinephrine increases the oxygen capacity of both arterial and venous blood, thereby indicating an increased blood flow, which they attribute to increased tone of the peripheral arteries. They speak of a "tightening up" of the blood vascular system with consequent increase in blood pressure. Unlike epinephrine, ergotamine also causes increased blood concentration. They suggest an increase in the tone of the arteries in general, rather than peripheral vasoconstriction.

Clinical Note

Factors influencing results.—The writer has analyzed factors which might influence results in the allergic treatment of migraine. Age was not a factor. Patients over sixty, even over seventy, were relieved on food avoidance. The duration of the disease was likewise of little importance. The maximum duration in the group of patients who were relieved was 55 years. That in those not relieved was 45. The average duration in the relieved group was 21 years, that in the unrelieved 15. These findings are comparable to those with the other allergic syndromes.

Forty-eight per cent of females were relieved, as contrasted with 60 per cent of males. The reason is conjectural. There may be an endocrine factor. Also men often experience less difficulty in following dietary restrictions than women. Fifty-two per cent of those with family allergic history were relieved, against 33 per cent without family allergic history. Of those with personal history or evidence of other allergy, 62 per cent were benefited; 37 per cent of those without other allergy were relieved.

When headache was usually or always bilateral, results were not as good as when it was unilateral (hemicrania). Other than this, location appeared to play no part. Prodromal symptoms occurred with equal frequency among those who were and those who were not relieved. Subjective ocular symptoms, especially flashes of light and hemianopia were rather more frequent among those not relieved. Women whose migraine always accompanied the catamenia were more often not relieved, although one in this group was relieved. There was in general no frequency distribution among prodromata, ocular symptoms, mental symptoms, vasomotor symptoms, paresthesias, frequency of attacks, duration of attacks, gastrointestinal or urinary symptoms that would enable one to predetermine whether a case of migraine or of chronic recurrent headache will or will not respond to allergic therapy. Furthermore, in both good result and poor result series, nonallergic factors were responsible for individual attacks in almost equal frequency. Poor result cases as well as good result cases may show personal and family evidence of allergy. It seems probable that allergy plays a part in many of the poor result cases and that as we learn more of migraine, allergic treatment will benefit a larger proportion. The writer observed good results in 51 per cent with entire relief in 40 per cent. In an

additional 17 per cent there was evidence of an allergic factor even though relief was not adequate. The average duration of relief in the series covered was 4.4 years, ranging from several months to 11 years.

In one survey the writer found 83 different foods which patients had found responsible for attacks. As in other allergic responses, nearly any food

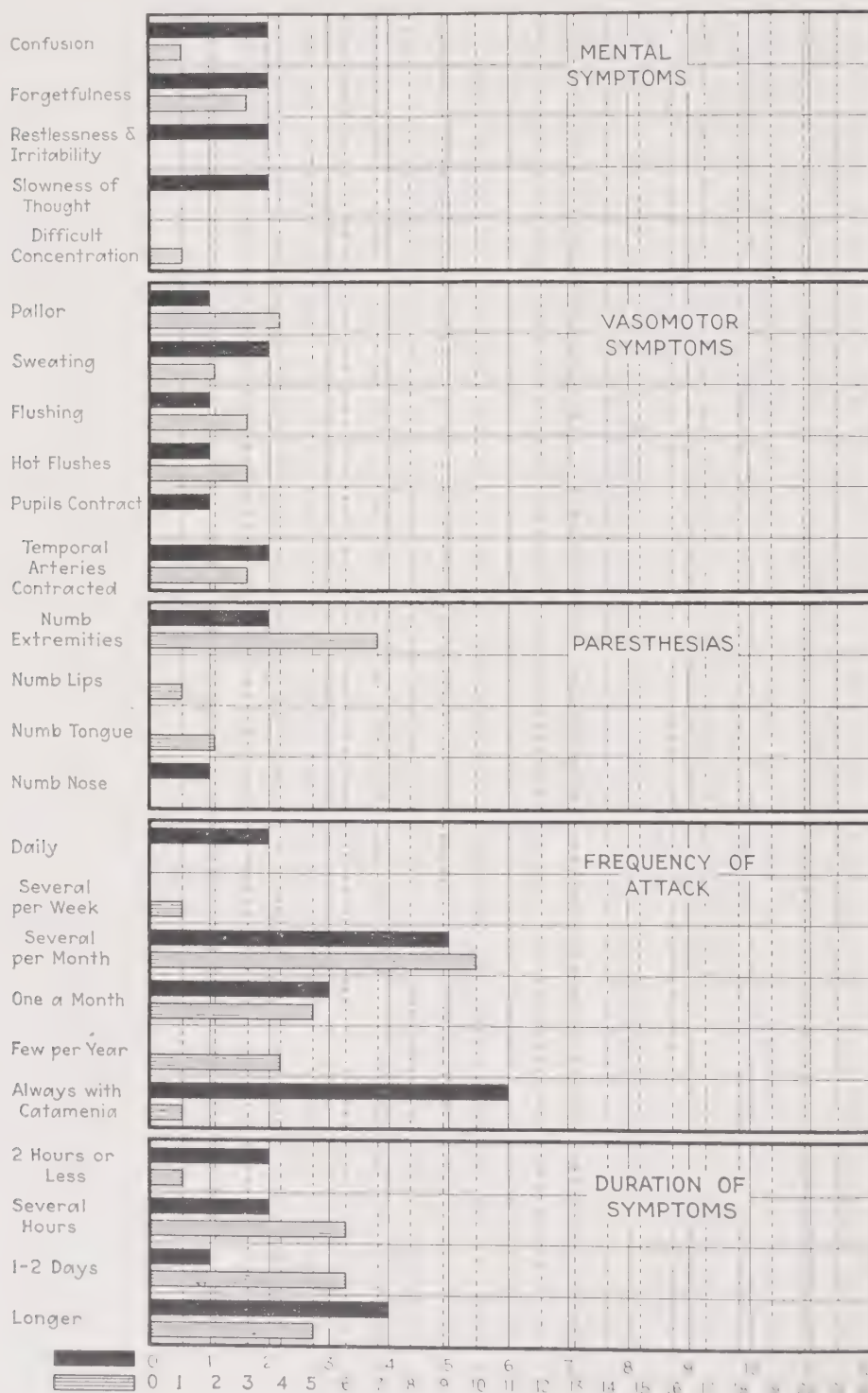


Fig. 320.—Migraine. The various factors analyzed appear to be of little significance in differentiating allergic from nonallergic recurrent headaches except that headaches occurring always with the catamenia are less responsive. Even so, some of this type do respond to allergic treatment.

may cause trouble. Chocolate, wheat, onion, cabbage, cucumber, apple, pea, banana, peanut, bean, celery, carrots, milk, pork, egg, turnip, lettuce and "candy" were the most frequent offenders.

Even in those who were not adequately relieved, it was found that specific foods sometimes caused headaches. Although allergy existed, other factors, probably nonallergic, caused symptoms to persist.

In a similar survey of 127 cases at the University of Michigan Hospital Sheldon and Randolph (1935) reached comparable conclusions. Thirty-seven per cent had suspected certain foods prior to study. These, in order of incidence were onion, bean, egg, coffee, tomato, meats, milk-cream, cabbage, peanuts, strawberry, radish, lettuce, asparagus, chocolate, apple.

TABLE LXXVIII.—FOODS CAUSING MIGRAINE

	POSITIVE REACTORS	CAUSED TROUBLE	DISCOVERED BY PATIENTS. TIMES MENTIONED
Wheat	19	19	
Rye	1	1	
Barley	1	1	
Oat	3		
Rice	2	1	1
Corn	4	2	
Coconut	1	1	
Pineapple	1		
Onion	6	4	2
Asparagus	5	2	
Banana	10	5	
Ginger	7	1	1
Fig	1		
Buckwheat	1	1	
Walnut	2		
Pecan	3		
Spinach	4	1	
Beet	4		
Turnip	7	2	2
Cabbage	6	2	
Cauliflower	4	1	
Kohlrabi	1	1	
Brussels sprouts	1	1	
Mustard	2		
Raspberry	2	1	1
Strawberry	4	2	1
Apple	6	3	1
Pear	6	1	
Almond	3	1	
Prune	2		
Cherry	4		
Apricot	2	1	
Peach	5	1	2
Pea	13	8	
Kidney bean		9	
Peanut	13		
Blackeye pea			
Lima bean		7	
Bean	13		2
Lemon	2	--	1
Grapefruit	3	--	1
Orange	4	1	
Grape		1	
Cottonseed	1		
Okra			

(Cont'd on next page.)

TABLE LXXVIII—CONT'D

	POSITIVE REACTORS	CAUSED TROUBLE	DISCOVERED BY PATIENTS, TIMES MENTIONED
Cocoa	12	8	
Tea	5	1	
Celery	10	2	
Carrot	10	1	
Sweet potato	4	2	1
Tomato	5	2	
Peppers	2	1	
Eggplant	1	1	
Potato	3	1	
Coffee	3	2	
Squash	6	1	
Cantaloupe	5	2	1
Watermelon	1	1	1
Cucumber	1		
Lettuce	6	4	
<i>Animal Foods:</i>			
Beef	1	1	
Veal	2		
Milk	9	9	1
Cheese	1	2	2
Egg	9	4	1
Chicken			
Pork	6	6	2
Lamb	4	2	
<i>Sea Foods:</i>			
Crab	--	--	1
Oyster	2	1	
Fish	2	2	
Sardine	--	--	1
Salmon	--	--	1
Tuna	1	1	
Shad	1	1	
<i>Miscellaneous:</i>			
Whisky	--	--	2
Acid foods	--	--	1
Chicken liver	--	--	1
Ice cream	--	--	2
Sweetbread	1		
Candy	--	--	8
Rabbit	--	--	1
Vanilla	1		

In a series of patients with migraine it was found that, of approximately 300 positive skin reactions about half or 150 were found to be of etiologic significance. In other words, we may assume that in a series of positive skin reactions only half of them may be of immediate allergenic importance.

In the same series the patients discovered by means of the food diary that an additional 60 foods which had failed to give positive skin reactions caused attacks.

This series illustrates the value of the combined use of skin testing and food diary. False positive and false negative skin reactions may be gradually accounted for by this method.

These authors observed a higher percentage of relief in the female series (72 per cent) than in male patients (48 per cent). Women with migraine accompanying the menstrual period received significantly less relief than women in whom there was no known association with the menses. In their series two-thirds of the patients (both sexes) experienced partial or complete relief on dietary avoidances.

Frequency of the migraine symptom complex.—In a survey of a community of 508 persons Vaughan found that 7 per cent had had chronic or recurrent headaches due to foods, and without exception could name the responsible foods. Another 7 per cent attributed their headaches to definite causes listed as follows: constipation, high blood pressure, gall bladder disease, fatigue, indigestion, sinus disease, eyestrain, asthma, catamenia.

In a series of 85 consecutive allergic patients complaining of asthma, hay fever, urticaria, eczema or gastrointestinal allergy seen during the winter of 1933 to 1934, 29 per cent had recurring headaches of the migrainous type. Sixteen per cent of the group with headaches had from their own experience recognized the foods causing headaches. These observations are not unlike

TABLE LXXIX.—NONALLERGIC FACTORS

REASONS GIVEN FOR ATTACKS	IN 7 GOOD RESULT CASES	IN 11 FAIR CASES		IN 20 CASES NOT RELIEVED	
		BY AUTHOR	BY PATIENT	BY AUTHOR	BY PATIENT
Unknown	--	4	1	11	3
Fatigue	5	--	--	--	8
Worry	1	1	1	--	4
Excitement	2	--	2	--	1
Nervousness	2	--	--	--	2
Constipation	3	--	3	--	3
Catamenia	--	--	1	--	1
Strong light	1	--	--	--	1
Sleeplessness	--	--	--	--	1
Hunger	--	--	--	--	1
Exertion	--	--	1	--	--
Eyestrain	2	1	1	--	--
Thyroid deficiency	--	1	1	--	--
Noncooperation	--	2	--	7	--
Colitis	--	1	--	1	--
Cholecystitis	--	1	--	1	--
Tuberculosis	--	1	--	--	--
Purpura	--	1	--	--	--
Dust	1	--	--	--	--
Tooth infection	1	--	--	--	--

In migraine as in allergic colitis and indeed in most allergic manifestations other nonspecific, nonallergic factors may interact to precipitate symptoms. The above list of nonallergic factors responsible for attacks of migraine is quite similar to the older lists of causes of migraine prior to the development of the allergic concept. The allergic predisposition may be looked upon as the common denominator.

In the above list the assignment of causes independently by the author and by the patients themselves reflects these two points of view. Thus, the patient would not recognize noncooperation and would be less likely to ascribe symptoms to other pathology such as thyroid deficiency, cholecystitis, etc. A combination of both series of explanations is probably more accurate than either alone.

the more recent ones of Alvarez and Sinshaw (1935) who found that among 400 persons with primary gastrointestinal complaints there were 59 instances in which the patient knew that certain foods caused headaches.

Notes on Treatment

Rowe, who has contributed much to the allergic study of migraine reported (1937) that among 247 patients treated with the elimination diet, 63.5 per cent had good results, 19.5 per cent fair, and 17 per cent failed to improve.

Wescott (1934) estimates that about 35 per cent of migraine is allergic and should respond to appropriate treatment.

Rinkel (1933) objects to the term allergic migraine. He states: "The hypothesis that migraine is an allergic disease cannot be maintained, unless there is proof, not only that allergens are responsible for attacks, but also that the mechanism of symptom production is that of atopic hypersensitivity. . . . There is yet to be found any one feature of the history or symptoma-

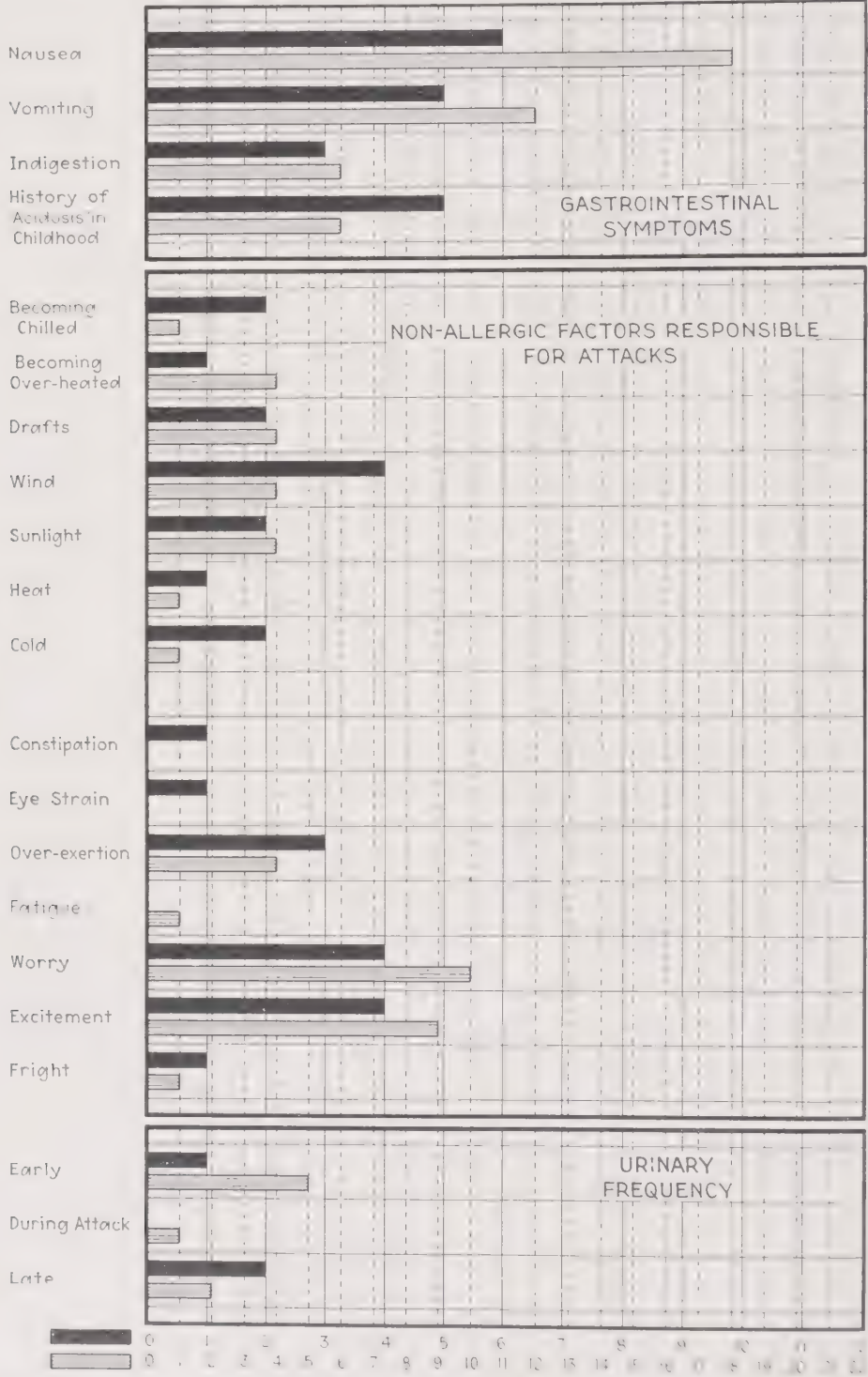


Fig. 321. Migraine. The various symptoms and factors recorded appear equally distributed among those who did and did not respond to allergic therapy. It should be noted that nonallergic factors may cause attacks in allergic as well as nonallergic migraine.

tology that indicates allergy as a factor in migraine. . . . The precipitation of migraine by various specific foods is not sufficient evidence to warrant the inclusion of migraine in the category of allergic diseases." Nevertheless he recognized the existence of an allergic headache. He describes many cases of relief of migraine by allergic methods and grants that allergy may be playing a part in the precipitation of attacks, but denies that migraine may be primarily an allergic condition.

He finds, as we have, that patients with regular periodicity do not respond as well to allergic therapy as those with irregular periodicity. He has reproduced cortical features (sensory, motor and vasomotor) by deliberate feeding. He finds that patients who knew before examination that some food or foods would cause headache obtained most benefit.

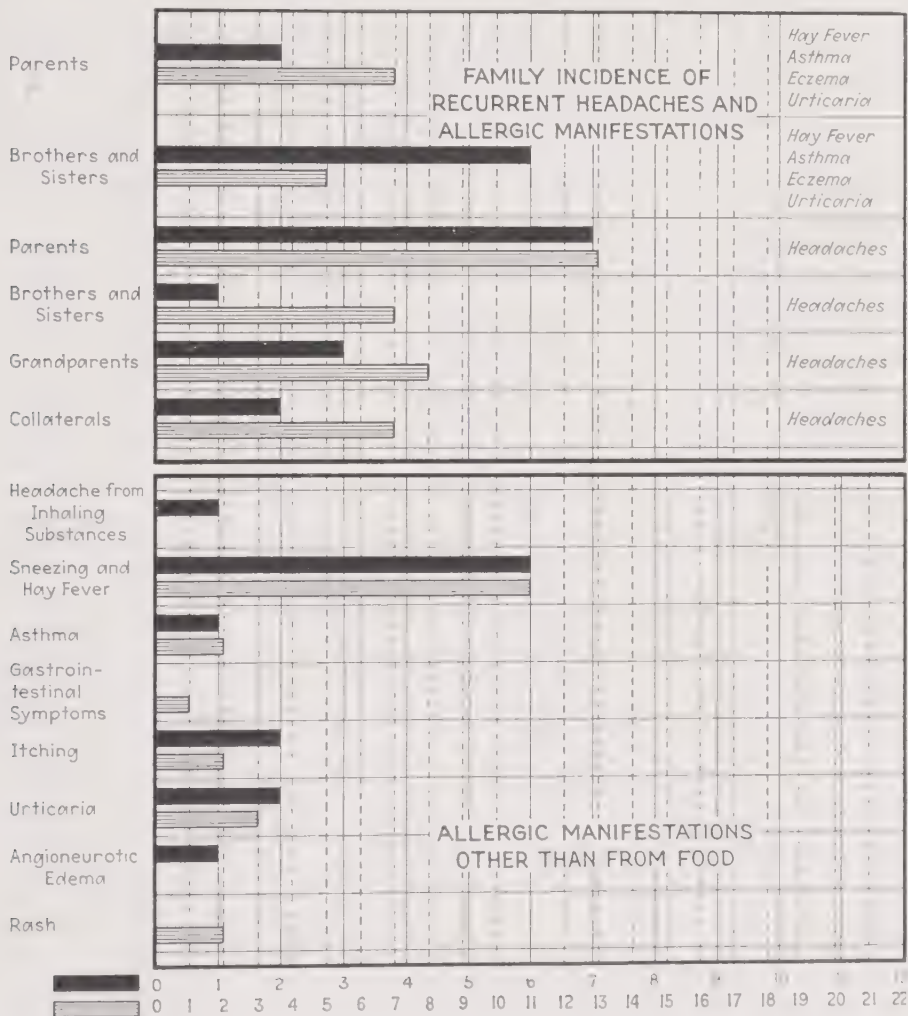


Fig. 322.—Family incidence of allergy and personal incidence of other allergic symptoms in migraine. Although all cases with migraine do not respond to allergic therapy, there is as high an incidence of family and personal allergy in those who do not respond as in those who do. This suggests that with improved methods more of the poor result cases should become good result cases.

In order that a patient may know what food is causing his symptoms, it must be one that is eaten only intermittently. Such patients may also be allergic to foods eaten daily. The person who knows beforehand that certain foods cause his headache will usually cooperate more enthusiastically and

more completely in an effort to find those offenders which are eaten more frequently. Cooperation on the part of the migraine patient is not always as easily gained as one would expect.

Rinkel remarks that ephedrine was tried in nearly all of his patients and was found to be of more aid than any other drug. However when it was of value, the response to allergic management was no better than the general average.

Rinkel describes a case in whom sensitization to different foods came and went with the lapse of months and years, so that a certain food at times would cause symptoms, later none. Foods in one year would cause headaches and in the next year, colitis or some other symptoms. We might term this phenomenon evanescent sensitization.

Alvarez spoke of migraine as "A Disease of Civilization" and thought it due to inadequate or abnormal reactions to the stress and strain of life. He recommended the use of oxygen and others since have confirmed this finding. It can be used with the B.L.B. inhalation apparatus.

Other Headaches

There is, at present, considerable variance in the views regarding the role of allergy in the production of migraine. The work of Wolff and others is thought by some to negate entirely the idea of an allergic mechanism. Others believe that many if not all migrainous headaches can be adequately cared for by proper allergic management.

It may be said with assurance that there are allergic headaches. Some of them show many if not all the stigmata of classical migraine while others bear no resemblance to the picture of migraine. Many headaches appear to be due to the use of certain foods and may be relieved by abstinence from them. We have never been able to determine any criterion by which one may determine whether a given headache is due to an allergic reaction. An allergic investigation may secure relief by finding and eliminating from the diet the foods to which the patient may be sensitive but there is nothing in the history of the disease which will help separate headaches into the allergic and nonallergic groups. It will be found that some of those which are clinically typical migraine may be on an allergic basis while some are not and the same statement may be made about other headaches not resembling migraine.

The point probably worth emphasizing is that migraine is not the one type of headache which is allergic. There are possibly as many nonmigrainous headaches which are allergic as there are those which are truly migraine. It is wiser to speak of allergic headache recognizing that many varieties will be included and which appear to have no relationship except their common etiologic mechanism.

Inhalant allergy and migraine.—Goltman emphasizes the concurrence of nasal symptoms with migraine. He finds that often the first sign of an oncoming headache is nasal congestion which subsides with subsidence of the headache. He believes that the inhalation of allergens may cause true migraine equally as well as the eating of allergenic foods. He has relieved migraine with injections of specific inhalant allergens including pollens, animal hair and dander, orris root and bacterial vaccines. He mentions "Ilytox" and other insect powders and sprays as causing migraine in one case. Relief followed avoidance. The elimination of inhalants alone does not always assure relief, specific hyposensitization being sometimes required in addition.

The writer has recently had occasion to confirm Goltman's claim that inhalant allergens may cause migraine. A woman with migraine and nasal allergy reacted to house dust. During the course of dust desensitization, attempts to increase the dose too rapidly invariably produced migraine. Further questioning then developed that she was likely to have attacks after dusting.

We have seen that inhalants such as silk may be responsible for dermatitis, the allergen being transported by the blood to the skin after absorption from the respiratory tract. The same may apply equally well in migraine. Goltman has demonstrated the rapidity with which material may be absorbed from the accessory sinuses by the injection therein of phenolsulphonphthalein which was found 10 minutes later in the urine.

It develops, then, that inhalant desensitization may sometimes be needed as adjunct therapy in migraine.

The writer has studied a woman who regularly developed migraine from the odor of several perfumes.

Another patient with headaches and allergic to feathers observed that when sleeping on feather pillows he usually developed low-grade nocturnal headaches. When avoiding feather pillows he did not.

CHAPTER LXXV

SKIN DISEASES

Historical notes.—Pusey states that the Hippocratic writings described *urticaria* from mosquito bites and from gastrointestinal disturbances. They also described universal exfoliative dermatitis with death. Celsus (first century A.D.) described *erythema multiforme* and connected it with rheumatism. Sydenham (1685) described urticaria as like the stinging of nettles. Juncker (1718) provided an adequate description. Jean Astruc (1684 to 1766) suggested that urticaria is a local obstructive edema. Willan (1757-1812), the accepted founder of modern British dermatology, provided the first comprehensive definition of eczema, a term used by the ancients. In 1814 Bateman remarked on the frequency with which urticaria was produced by certain foods such as shellfish.

From Willan to Hebra, through the first half of the nineteenth century, the concept of *eczema*, so clearly outlined by the former in 1800 again became confused, especially through the writings of the French dermatologists who applied the term far too loosely. Hebra, the first great dermatologist of the Vienna school, applied the newer methods of cellular pathology to diseases of the skin. He inaugurated the anatomico-pathological period in dermatology. Although he did not deny the systemic origin of skin diseases and indeed emphasized the importance of internal disease in urticaria and pruritus, he differed from the contemporary French school which dwelt on the importance of constitutional dyscrasia, in that he placed greatest emphasis on local factors. He demonstrated the growth of the fungus of *ringworm* in the epidermis and resurrected Willan's concept of eczema as a predominantly local disease. Chief progress during the second half of the nineteenth century was in study of the histology and micropathology of the dermatoses. An increasing number of diseases were differentiated from one another. The local skin infections, especially those of fungus origin, were placed in a class by themselves.

Angioneurotic edema, often called Quincke's edema, was described by at least six writers prior to Quincke's report in 1882. The earliest according to Bray was that of Stolpertus (1778). Dinkelacher (1882) mentioned the hereditary factor, which was firmly established in the writings of Osler (1888). The term angioneurotic edema, like neurodermatitis, is not altogether consistent with modern understanding of the condition and might possibly better be supplanted by Quincke's original designation, "acute circumscribed edema."

Pathology

For a clear understanding of the differential pathology of contact dermatitis and atopic dermatitis or urticaria one need but recall the method by which the antigenic material comes in contact with the skin, whether externally or through the blood. The differential pathology has been very clearly described by Sulzberger, Wise and Wolf. The eczematous or contact reaction takes place in the epidermis and is characterized especially by spongiosis and vesicle formation in the epithelium. The urticarial reaction takes place beneath the epidermis, in the cutis, and is characterized by extravasation of fluid with edema and eosinophile accumulation. The delayed or tuberculin type reaction occurs in the cutis and is characterized by lymphocyte infiltration, with the subsequent accumulation of epithelioid cells. The drug eruptions and the "ids" (the eczematous rashes accompanying fungus infection and some bacterial infections), may partake of any of these types, involving the deep cutis, the epidermis or the hair follicles, producing nodules, fixed areas, multiform dermatoses or follicular lesions.

Clinical Manifestations

Dermatitis.—This has been sufficiently discussed in preceding chapters. Contact dermatitis usually appears on exposed areas, often with associated vesiculation. Atopic dermatitis is classically present on flexor surfaces espe-

cially the neck, the bends of the elbows and the popliteal spaces. Both may involve the face. Seborrheic dermatitis is the most important skin condition to be differentiated, especially in children. Sulzberger states that in infants it is often extremely difficult and in many cases utterly impossible to differentiate the three groups.

The fixed drug eruptions are usually quite characteristic and relatively easy of identification provided one is mindful of their possible presence. Fungus eruptions, especially of the "id" type, may simulate other forms so closely as to render differentiation difficult. The finding of a local nidus of infection and a positive trichophyton or monilia albicans (oidiomyces) skin reaction aid in the differentiation. The fungus is not found in scrapings from "ids."



Fig. 323.—Dermatographia.

Urticaria.—Urticaria has been described as the *bête noir* of allergists. Our own experience has probably been very much like that of others, that either one promptly finds the allergic cause and promptly obtains most satisfactory results or, this failing, it becomes a long drawn out process, sometimes terminating in success, often in failure.

Fink and Gay (1934) observed 170 cases of urticaria and angioneurotic edema over periods from 2 to 10 years. Sixty-nine per cent were females. The average duration prior to consultation was 4 years, the usual age in the fourth decade; 15 per cent presented an allergic personal history, 28 per cent an allergic family history; 73 per cent gave positive skin reactions, the significance of which was often problematical. The authors divided the cases into five groups depending upon the findings and the results of treatment.

1. The first comprised those associated with focal infection (30 per cent). About half of these were operated upon for removal of infection and of these 74 per cent were reported cured.

2. The allergic group comprised 20 per cent of the series; 75 per cent of these were symptomatically cured by avoidance.

3. The psychogenic group represented 18 per cent.

4. The endocrine group accounted for 5 per cent of the series, and in these the symptoms were associated with menstruation, pregnancy, menopause and hypothyroidism.

5. The remaining 25 per cent were designated as of undetermined etiology.

The authors stressed the importance of not considering all cases of urticaria and angioneurotic edema as allergic.

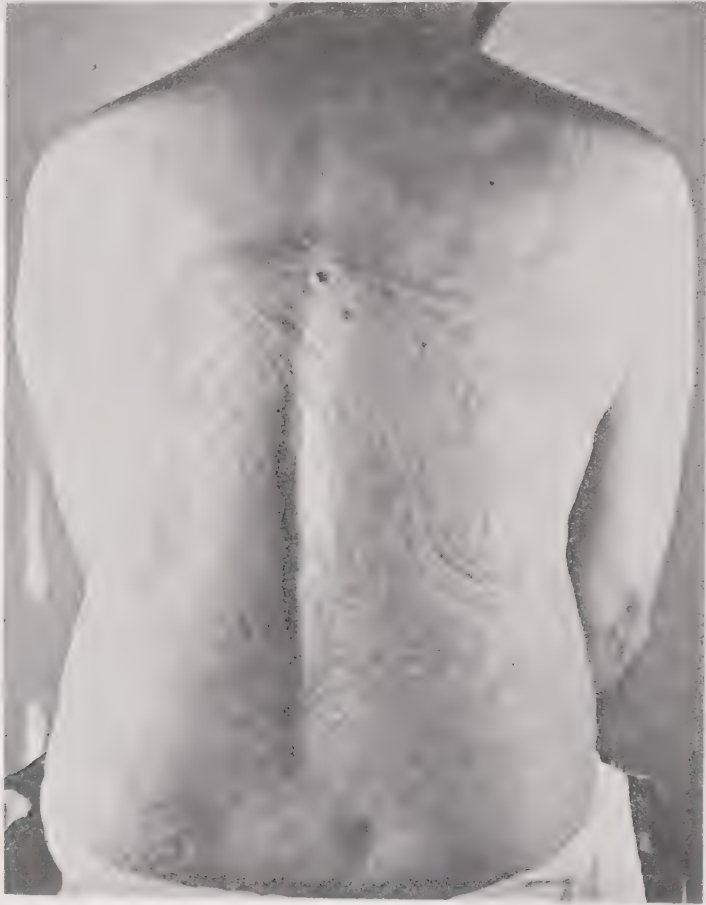


Fig. 324.—Dermographia from scratching.

Black (1944) stated that approximately one-half of the urticarias which he saw could not be proved to be allergic. The figures will vary with different observers, but all will agree that a considerable number cannot be shown to be on an allergic basis.

The cases in whom the etiology is proved may be classed as those due to:

1. Food
2. Drugs
3. Sera
4. Antibiotics
5. Infection-bacterial
6. Infection-protozoal, e.g., malaria
7. Infestation with parasites on skin

8. Endocrine
9. Contact with danders or vegetable irritants
10. Emotional trauma
11. Animal parasites
12. Physical agents

The per cent of patients in each of the above classes will vary widely with different workers. Some will insist that all chronic urticarias are on an emotional basis while others will state that this group includes few. All will agree that there is an increasing incidence of urticaria resulting from the indiscriminate use of sera, sulfonamides, and antibiotics. Those due to drugs may not be more frequent. It may well be that we are recognizing them more frequently. Geographical differences may play a part. Urticaria associated with chronic malaria is seen in the South and scabies as a cause of urticaria is fairly common in areas where cleanliness is considered an affectation.

Seasonal urticaria may occasionally be seen as a result of sensitization to pollen. It may occur as an accompaniment of hay fever or more often is found alone. In these patients the skin and not the nasal mucosa appears to be the shock organ. Treatment is the same as for seasonal hay fever.

In 40 cases of urticaria Crip (1932) found no definite disturbance in acid-base balance or carbon dioxide combining power of the blood. Blood sugar, nonprotein nitrogen and urea were normal. Uric acid was slightly elevated and blood chloride slightly diminished during an acute attack. Blood calcium was normal.

Angioneurotic edema.—This is a not infrequent finding in allergic practice, usually associated with other allergic manifestations, most frequently urticaria. It may be due to foods, either following digestion or by contact absorption through the oral mucosa. It may occur, like urticaria and atopic eczema, following inhalation. It may be acute or chronic.



No. 225.—Angioneurotic edema of left cheek. As indicated in this figure it need not be of extreme degree.

Angioneurotic edema is said to involve chiefly the soft tissues such as those of the face, genitalia, etc. We might say more accurately that it is observed more easily in these areas. The visceral manifestations may be very deceptive. Headache, often severe, is a frequent concomitant. Bassoe has reported a case in which the neurologic findings suggested brain abscess and the patient was subjected to decompression. The only findings were localized edema and hyperemia.

Abdominal symptoms are frequent, with severe generalized pain, vomiting, hematemesis, melena, and even abdominal rigidity. Here again surgery has been resorted to and in this way it has been demonstrated that the local lesion is an edema of the intestine. Occasionally such an edema is accompanied or followed by intussusception for which surgery becomes urgently necessary.

While angioneurotic edema of the respiratory tract is more frequently recognized, for it involves the larynx and higher structures, the probability is that it occurs within the lungs and bronchial tree much more frequently than suspected. Long ago, Osler described the appearance and disappearance of rales in one of his cases of angioneurotic edema and mentions pneumonia as one of the complications. Vaughan and Hawke described a case with roentgen changes which, by the rapidity of their disappearance, were interpreted as due to angioneurotic edema. Feer described a case with generalized rales throughout both lungs which disappeared rapidly within 24 hours. Cole and Korns (1934) consider Löffler's cases of transient infiltration of the lungs as presumably due to angioneurotic edema. They describe a child with recurring angioneurotic edema who also had recurring attacks of severe frontal headache with shortness of breath and fever. Roentgenograms showed evidence of bronchopneumonia which they interpreted as due to angioneurotic edema. There was a leukocytosis ranging from 6,000 to 62,000 and an eosinophilia of from 54 to 84 per cent. Their case suggests that many so-called bronchopneumonias in allergies may be angioneurotic edema. It should be borne in mind that visceral manifestations of this malady may occur in the absence of cutaneous symptoms.

Papular urticaria. Prurigo mitis.—Papular urticaria or lichen urticatus usually occurs in childhood, is distributed rather symmetrically on the outer aspects of the arms and legs and the buttocks, with occasional scattered lesions on the face and trunk.

The characteristic primary lesion is an erythematous patch one-fourth to one-half inch in diameter, only slightly elevated, and surmounted by a central conical, usually follicular papule, the size of a millet seed, deep red in color. Pressure with a glass shows the typical pale ivory color of urticaria. Vesicles sometimes occur, and scratching due to the intense itching often results in excoriation. During resolution of the lesion it often becomes flattened, smooth, shining, lichenoid. Occasionally there is an accompanying urticaria or angioneurotic edema. After the individual lesion has lasted a few minutes to several hours, the erythema disappears but the papule may persist as long as a week or more. A faintly pigmented spot remains for a short time thereafter.

Individual lesions appear in crops, usually beginning during the night. Different stages of evolution may be seen at one time. The condition may persist for months or years, although the individual attacks usually last a matter of days. Occasionally there is seasonal remission, usually in the summer.

Prurigo mitis is a similar skin disease which usually begins during the first year of life and is indistinguishable from papular urticaria in its early stages. After several months the characteristic prurigo papules appear. These are hard, round or conical, the size of a millet seed and are either of normal skin color or slightly reddened. There is no surrounding erythema. There may be few or many papules. They are accompanied by intense pruritus. As new crops come, the urticarial element gradually disappears. After the condition has persisted a year or two pigmentation gradually appears. Scars result from scratching. Papules persist. The distribution is on the extensor surface of the extremities. Flexor surfaces are not involved. The forehead is sometimes involved. The skin in the diseased areas is rough, dry, fissured and thickened. There is sometimes slight scaling. The feel of the skin is like that



Fig. 326.—Chronic angioneurotic edema of the lower lip associated with allergy to a number of foods. Their avoidance resulted in about 50 per cent improvement (right), but did not cure. Local tissue pressure was elevated to six times that in her unaffected skin.

of a nutmeg grater. Occasionally there is some weeping. The regional lymph glands are always enlarged. There may be remissions. This is more likely to occur in the winter. The disease tends to disappear before adolescence.

Various investigators have suggested an allergic etiology. Some have reported relief by avoidance of positively reacting substances, while others state that although positive reactions have been observed no relief has followed avoidance.

Walzer and Grolnick (1934) studied 36 children with papular urticaria and 5 with prurigo mitis. They found a high personal and family allergic incidence and often found positive sensitization reactions but were unable to relieve the disease by allergic methods. They conclude that both conditions are probably atopic, but that the positive skin tests observed bear no relation to the skin lesion. They believe skin testing in the presence of these lesions is of no diagnostic or therapeutic value.

Sulzberger (1933) points out that positive skin reactions are present even though no benefit can be obtained following specific avoidance. However, if the child eats a substance to which he has given a positive skin reaction, his symptoms become more pronounced.

These two diseases appear to merit further study, as allergic methods become improved. The similarity in character and distribution of the skin lesions of avitaminosis A and prurigo mitus is of interest.

Pruritus.—Simple pruritus has occasionally been mentioned as allergic in origin. Rowe mentioned itching of the nasal and oral cavities in asthma; allergic pruritus ani and pruritus vulvae. Balyeat has described pruritus of the neck and chest as characteristic of asthma, and Wynne has described two cases of senile pruritus due to the ingestion of wheat. Mittelman has described pruritus in a psychoneurotic individual who produced self-inflicted



Fig. 327.—Allergic factor in nonallergic conditions. Psoriasiform dermatitis in a food allergic, about 50 per cent relieved with dietary restrictions.

wounds in itching areas. She had seen many physicians, none of whom had helped her until she was found allergic to pork, cabbage, lamb, chicken, salmon, tuna, corn, cod, shrimp and carrots. Their avoidance relieved her subjective cutaneous symptoms. This did not cure her psychosis but the latter was sufficiently improved with psychotherapy that she ceased to produce self-inflicted wounds.

The writer found that about one-third of a series of pruritus ani and perianal eczema in which no other local cause could be found responded satisfactorily to allergic dietary avoidances.

On the whole we have had very little success with simple pruritus without objective skin lesions except in those obvious cases in which the wearing of wool or some other article of clothing was responsible.

Erythema multiforme.—This is often allergic, being especially characteristic of drug allergy.

Psoriasis.—From time to time the suggestion is made that psoriasis may be an allergic manifestation. Zeigler (1931) observed that a number of hay fever patients also suffered from psoriasis, and that with pollen treatment the latter tended to clear up. He then tested a series of psoriatic patients with pollens, finding some positive reactions. Twenty-two per cent of the psoriatics also had hay fever. Treatment with pollen extract caused appreciable improvement in the psoriasis.

I have not tested psoriatics with pollens, but have studied them from the point of view of possible food allergy, and the results have been consistently disappointing. A psoriasiform lesion of the right elbow in a boy of twelve disappeared after he discarded a leather wind breaker coat. Twenty-four-hour patch test was negative. The distribution of the lesions of psoriasis on areas which are especially likely to come in prolonged contact with and to be rubbed by clothing (possibly excluding the scalp) suggests that this possibility is worthy of further study. Suggestions concerning a possible relationship between psoriasis and sensitization to monilia have not borne fruit.*

Acne.—Rowe (1931), describing the treatment of a case of canker sores with the elimination diet, stated that a long-standing acne cleared up at the same time.

White's (1933) patient with long-standing acneform dermatitis, with typical distribution but without comedones and without seborrheic dermatitis, was relieved with the elimination diet. He remarks that although cutaneous tests were of limited value in this particular case they were of marked aid in that egg and wheat were found positive by this method. Following subsequent study with the elimination diet, peaches were also found responsible.

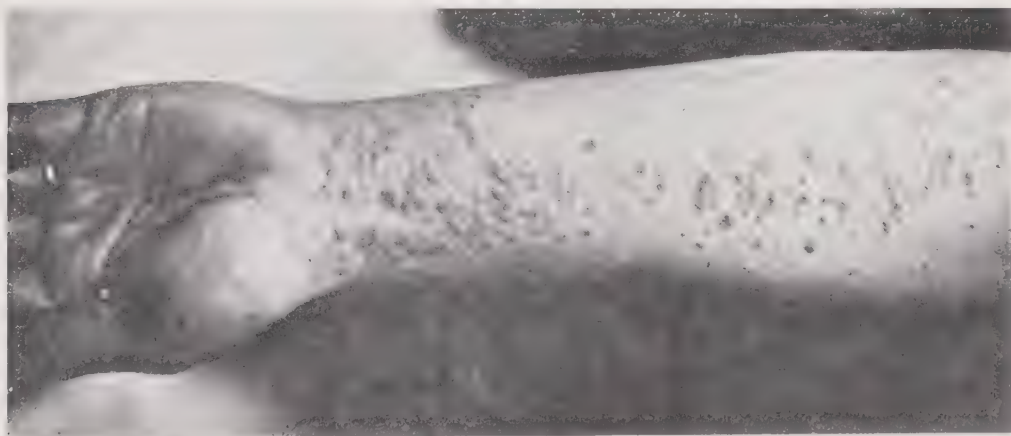


Fig. 328.—Differential diagnosis of an allergic dermatitis. Case of lichen ruber planus which, however, reacted to egg and was at least 50 per cent improved following egg avoidance.

He later reported (1934) a series of 32 cases with recurrent papular and papulopustular eruption of the body involving the areas in which acne vulgaris is ordinarily found. He described this series as acneform and differentiated them from acne vulgaris by the fact that in the former there were no comedones, no seborrhea of the face or scalp and no response to the usual acne therapy. Most of this group had had such therapy, including x-ray treatment, low carbohydrate diet, low fat diet, endocrine studies and removal of foci of infection.

*Stokes, John, Philadelphia. Personal communication.

White relieved these cases with the Rowe elimination diet. He did not derive much help from skin tests. He found that the commonest offenders were chocolate, milk, wheat, oranges, tomatoes and nuts. Some showed multiple food sensitization. Others reacted to food combinations.

Cunningham and Mendenhall studied 42 patients with acneform lesions. Each reacted by skin test to several foods. Patch tests were negative. Allergic dietary treatment gave over 90 per cent relief to 51 per cent of patients. An additional 13 per cent received from 70 to 90 per cent relief while only 13 per cent were not benefited. Attempts at desensitization with wheat extract in two cases produced considerable benefit in one. In both cases overdosage caused flare-up of the acne lesion.

My own experience with acne has not been as satisfactory. We usually observe positive skin reactions, especially to foods, but appropriate dietary restrictions rarely result in more than from 25 to 50 per cent benefit. We have found that the eating of chocolate so consistently results in a new crop of pustules that this food is interdicted in all cases of acne even though skin reactions may be negative. In my experience there is ample evidence of an allergic factor in acneform dermatitis, especially as indicated by flare-up following the eating of allergenic foods, but their avoidance does not usually cure.



Fig. 329.—Importance of differential diagnosis. Woman with allergic dermatitis of the hands who later came in with a swollen erythematous condition of the nose. The condition resembled beginning erysipelas, temperature was found to be elevated, and, in spite of other allergic skin pathology, treatment for erysipelas was instituted. The acute illness ran the typical course of erysipelas.

Skin tests with foods are of very little value in acne. If an investigation is considered advisable the use of elimination diets will be helpful for proper manipulation of the diet will prove whether there is any food sensitivity of clinical importance. Our results have been too poor using skin tests to have us feel justified in putting the patient to the expense of having them done. Manipulation of the diet may be done much more economically and, if the results are negative, as they usually are in our experience, the patient has not suffered any financial reverse in discovering them.

The occurrence of acne especially during adolescence, its frequent exacerbation with the catamenia, and the frequency of menstrual disturbance in those with the disease, together with the local lesion, hyperkeratosis, all suggest an endocrine factor. Treatment with various endocrine products has not yielded results better than the usual methods of treatment. At one time or another every glandular product available has been used and sometimes enthusiastically endorsed. None has withstood the impact of careful investigation.

Purpura.—Alexander and Eyermann (1927) reported 3 cases of purpura associated with allergy. Two years later they described 6 additional cases of allergic purpura due to food allergy. Barthelme (1930) reported purpura due to allergy to wheat and egg yolk. Allergic purpura, usually due to foods or drugs, must be recognized as a clinical entity. Cazort (1933) reports purpura associated with chronic malarial infection. The purpura partook somewhat of the nature of a fixed drug eruption in that it always occurred on the hands. The condition was controlled with quinine, later recurred with return of the malaria and again was controlled by quinine therapy. Cazort believes that this is allergic, on the same principle that Eyermann and Strauss (1930) feel that urticaria associated with malaria should be considered allergic.

These were cases of the Schoenlein-Henoch type, in which increased capillary permeability is the predominant or only hematologic manifestation. Thrombocytopenic purpura with its pronounced drop in platelets and associated effect on bleeding time and clot retractility has also been reported as allergic at times. Peshkin and Miller have reported thrombocytopenia from quinine and ergot while Loewy has described thrombocytopenic purpura from sedormid, which could be produced at will by taking a four-grain tablet. Squier and Madison have described 6 cases due to foods, in 3 of which thrombocytopenia or purpura or both could be produced at will by food ingestion. The foods included Irish potato, milk, wheat and egg. Rappaport has observed a similar case due to onions, almonds and members of the cabbage family.

Squier and Madison also described a woman with menorrhagia during the course of pollen therapy in whom no local etiology could be found but in whom a definite drop in thrombocytes and leukocytes with rise in eosinophiles occurred following injections of pollen extract. Her menorrhagia cleared up after termination of pollen therapy.

Rappaport describes several cases who have not shown changes in the thrombocytes but who had severe hemorrhages from the nose, the rectum, and the vagina following the ingestion of allergenic foods.

Cohen has noted the frequency with which allergic patients bruise easily. This has likewise been my experience. Many of the bruises are spontaneous. Appearing solitary and occurring only at long intervals with no other evidence of illness, they scarcely justify the designation purpura.

CHAPTER LXXVI

GASTROINTESTINAL ALLERGY

Lucretius (95-56 B.C.) wrote that one man's food might be an intense poison for another. Before him, Hippocrates recorded his observation that cheese does not prove equally injurious to all men. - I imagine that since men first reached that stage where they could compare experiences, food idiosyncrasy has been a recognized entity. The interpretation of these isolated individualistic manifestations has necessarily varied at different epochs, depending upon the medical teachings of the day, some of which have persisted and still color our dietary proscriptions. Such is probably the popular belief in poisonous combinations of otherwise harmless foods, as seafood and cream, eaten at the same meal. Many of the arbitrary diets for gall bladder disease and colitis still found in modern textbooks would appear to be based upon cumulative past experience with cases of food idiosyncrasy. New discoveries in medicine have successively been applied in explanation. These have run the gamut from the ancient humors to gastrointestinal infection, ptomaine poisoning, and now, allergy.

Gastrointestinal allergy is usually a manifestation of food allergy, although not necessarily so. It may follow the ingestion of drugs or the hypodermic administration of allergenic materials such as drugs and pollen extracts.

Gastrointestinal Symptoms

Anaphylactic Shock.—The “grande anaphylaxie” of the French so well described by LaRoche, Richet and Saint Girons is the most startling and tempestuous of the responses to allergenic foods. Fortunately it is exceedingly rare. It consists in a severe acute reaction following ingestion, with nausea, vomiting, diarrhea which is sometimes bloody, violent pains, often urticaria, circulatory collapse and even death within minutes or hours.

Acute Food Allergy.—Probably the two most nearly pure allergic responses are the gastric, with nausea, vomiting and sometimes diarrhea, occurring promptly after eating the food; and the delayed or colonic response, with allergic colitis usually of the mucous type. Often the gastrointestinal disturbances are accompanied by other allergic symptoms. Acute angioneurotic edema of the lips and mouth following contact with foods also falls in this class.

Subacute and Chronic Gastrointestinal Allergy.—The following diseases or disease manifestations referable to the gastrointestinal tract may be due to allergy. None are always or invariably allergic but, when due to other causes, allergy must be considered as a possible secondary factor.

Cheilitis	Acute abdominal crises
Angioneurotic edema	especially accompanying purpura,
Canker sores	angioneurotic edema and urticaria
Nausea and vomiting	Diarrhea
Celiac disease	Spastic constipation
Cyclic vomiting	Mucous colitis
Pylorospasm	Pruritus ani
	Perianal eczema

Food allergy may complicate the picture of peptic ulcer, cholecystitis and appendicitis, the allergic reaction causing an exacerbation of the classical symptoms of these maladies.

Rowe has listed symptoms complained of among 150 cases of gastrointestinal food allergy as shown in Table LXXX.

TABLE LXXX. DETAILED ANALYSIS OF SYMPTOMS IN 150 CASES OF GASTROINTESTINAL FOOD ALLERGY

GASTROINTESTINAL SYMPTOMS:	PER CENT	PAIN AND SORENESS IN:	PER CENT
Canker sores -----	13	Epigastrium -----	27
Coated tongue -----	18	Upper right quadrant -----	17
Heavy breath -----	11	Upper left quadrant -----	3
Distention -----	35	Midportion of abdomen -----	19
Belching -----	34	Lower part of abdomen -----	22
Epigastric heaviness -----	17	Colonic soreness -----	17
Sour stomach -----	21	Ulcer type of pain -----	6
Burning, pyrosis -----	20	<i>General symptoms:</i>	
Nausea -----	46	Toxicity -----	25
Vomiting -----	27	Weakness -----	27
Diarrhea -----	16	Irritability -----	15
Mucous colitis -----	14	Nervousness -----	25
Constipation -----	39	Mental dullness and depression ---	24
"Gas in bowels" -----	19	General aching -----	13
Pruritus ani -----	5	Fever -----	5

The chronic manifestations of allergy may be bad breath, coated tongue, anorexia, flatulence, eructation of gas, vague abdominal discomfort. Sometimes there is definite mimicry of the symptom complex of cholecystitis or appendicitis, and these may be the patients who, after removal of these organs, continue to have their symptoms as before.

Diagnosis

One might feel that the differential diagnosis of gastrointestinal allergy should be a simple procedure. As a matter of fact those who have seen abdominal allergies with one or more telltale scars from mistaken surgical diagnosis realize how frequently the symptoms may resemble those of organic disease.

The first requisite in diagnosis is the realization that allergy may be responsible for a given set of symptoms. Following this, appropriate allergic studies as outlined in the first portion of this book will prevent most of the pitfalls.

If it is remembered that we are not dealing with a disease entity but a reaction which may occur anywhere along the gastrointestinal tract and that the symptoms produced are dependent upon the location and intensity of the reaction, it is apparent that a definite diagnosis may be difficult. It should be kept in mind, too, that the mimicry of allergy is practically never perfect and it should be given consideration whenever the clinical picture of organic disease is not clear cut.

The second requisite is a sufficiently comprehensive medical study which includes physical examination, routine laboratory procedures, usually gastrointestinal x-rays and often gastric analysis, biliary drainage and examination of the feces. This not only protects the surgeon against needless surgery but also the allergist against failure to recognize organic pathology which should be treated. There is no characteristic x-ray picture of gastrointestinal allergy but the information gained is often indispensable.

For additional discussion of gastrointestinal allergy, see p. 149.

CHAPTER LXXVII

CARDIOVASCULAR DISEASE

Thromboangiitis Obliterans.—Harkavy has found 87 per cent of thromboangiitis obliterans patients allergic to tobacco extract. Only 16 per cent of male cigarette smokers used as controls were allergic. Thirty-six per cent of smokers with coronary artery disease were allergic to tobacco. The average age of the patients who reacted to tobacco was 45. The average age of those with coronary disease who were smokers but failed to react to tobacco was 60. The inference might be drawn that tobacco allergy caused the appearance of symptoms at a much earlier age.

Sulzberger has found 77 per cent of thromboangiitis obliterans cases tobacco sensitive as against 28 per cent of the general hospital population. He found no special increase in arteriosclerotic heart disease (17 per cent), or in rheumatic heart disease (26 per cent).

Harkavy, in a later report, based on 103 cases of thromboangiitis obliterans, 319 male controls and 126 female nonsmokers, found 86 per cent positive reactions to tobacco among the cases of thromboangiitis against 20 per cent positive among control smokers.

Among the 65 control smokers who did react to tobacco he found that 47 were suffering from either angina pectoris or peptic ulcer. He then studied a series of 71 males with coronary artery disease, all of them smokers, finding 43 per cent reactive to tobacco. One-third of them gave positive family or personal allergic history.

He next studied 60 cases of peptic ulcer, finding that 26 per cent reacted to tobacco. Eighteen per cent reacted to pollens and many of them gave history of asthma and hay fever. Among 126 adult nonsmoking females only 12 per cent reacted to tobacco.

Some gastroenterologists, apparently for empiric reasons, have for years prohibited patients with peptic ulcer from smoking tobacco. The possibility that allergy to tobacco may sometimes be a factor in the causation of this disease, as suggested by Harkavy's researches, is interesting.

Harkavy finds that the tobacco extract which gives the best and most reliable positive reactions is one which has been first extracted with a mixture of alcohol and ether to remove most of the nicotine and undesirable coloring matter and which is then dialyzed for a considerable time in Coca's fluid. For intracutaneous testing this is first diluted ten times, because the original solution is irritating and produces false positive reactions.

Sulzberger presents 6 immunologic concepts in substantiation of his contention that thromboangiitis obliterans may be an allergic manifestation. These are general concepts which would apply to other allergic manifestations and are worthy of study.

1. Hypersensitivity may be localized in certain tissues and may be fixed in those tissues. Examples are seen in the dermatophytids of the hands and in the fixed drug eruptions. Phenolphthalein eruption usually occurs as a round or oval sharply circumscribed area, often located in the region of the genitalia or even on the glans penis alone. The arsphenamines, bromides and iodides have similar different predilections.

2. Certain allergens appear by predilection to sensitize only certain tissues and to call forth reactions in those tissues, to the exclusion of other tissues. This is well known in allergy. The drugs mentioned above may be cited as examples. Other examples are the skin rash due to quinine, shellfish, strawberry, or headaches due to onions.

3. Not only sudden and evanescent reactions are caused when the excitant meets the specifically sensitized shock tissue, but also chronic reactions. Permanent organic damage is often caused by one or successive shocks resulting from these encounters. The Arthus phenomenon is the most outstanding example. This is accompanied by vascular thrombosis and obliteration, with resulting necrosis. Other examples are found in the ulcerating iododermas and bromodermas.

4. An allergen which causes pronounced reaction in the specifically sensitized individual is harmless to one who is not so sensitized. This concept is generally accepted.

5. The vascular system in man appears to be peculiarly susceptible to sensitization and is the most frequent site of reactions. This is true in the phenomenon of smooth muscle spasm in experimental anaphylaxis. In dermatology Sulzberger cites as examples of vascular allergic reactions: erythema nodosum, follicular trichophytids and tuberculids, purpura, angioneurotic edema, urticaria and disseminated neurodermites.

6. The skin constitutes an excellent test tissue in a great variety of hypersensitivities of internal organs. This may be due to the fact that the vascular distribution in the skin permits direct testing of vascular response.

Having stated his 6 concepts, Sulzberger presents his evidence conforming thereto and indicative of allergy to tobacco. He found over 78 per cent of patients with thromboangiitis obliterans reactive to tobacco as against 36 per cent among healthy adult smokers, and 16 per cent among nonsmokers. Patients with thromboangiitis obliterans may also be allergic to foods or other inhalants and these allergic reactions may play a part. This would account for the occurrence of the disease in nonsmokers. He states definitely that discontinuance of smoking results in amelioration of the disease.

In his series with thromboangiitis obliterans and positive skin reactions he usually found no other positive allergic history or family history and was unable to transmit the sensitization by passive transfer, except in one case. He found that the allergenic substance was not nicotine. Although he has seen many hundreds of positive reactions to tobacco, he has seen only two to nicotine.

Harkavy has (1938) presented experimental evidence confirmatory of his claim that sensitization may occur locally in tissues such as the blood vessels. He produced gangrene of the toes of male rats by daily injections of denicotinized tobacco. He then showed by the Schultz intestinal strip method that the animals were sensitized to tobacco. Only half of another series of male rats injected with tobacco and who did not develop gangrene of the toes showed evidence of tobacco sensitization. Female rats did not develop gangrene of the toes nor did they show subsequent evidence of tobacco sensitization.

Alexander raises the question whether proof of tobacco sensitization by the uterine or intestinal strip method can be taken as proof that the local lesion in the toes was allergic. Chobot (1935) found positive tobacco reactions in nonsmokers and in children, ages 3 to 12. He suggests that much of the so-called positive tobacco skin reactions may be nonspecific. These observations bring us to the conclusion that there is evidence strongly suggestive of tobacco sensitization as an important etiologic agent in thromboangiitis obliterans, but that final proof must await further confirmatory studies.

Coronary artery disease. Werley appears to be the first to have suggested that food allergy may be a factor in the causation of angina pectoris and possibly also a provocative factor in coronary occlusion. Among 62 cases with angina

and coronary infarction 97 per cent were allergic to one or more foods. He calls attention to the frequent association of angina and migraine (55 per cent in his series). He relieved a number of cases of their angina by specific food avoidance.

While other observers have not confirmed this high incidence of food allergy in angina, it seems probable that it may act as an exciting factor in some cases. The writer has followed three persons for long periods in whom angina has been relieved in great measure on allergic dietary avoidance. None has been cured.

CASE REPORT.—A physician, aged 49, had a mild coronary thrombosis in 1929. At that time electrocardiogram showed an inverted T wave in Lead I, diphasic in Lead II. He was next seen in December, 1933, with daily attacks of angina. He had been taking nitroglycerin and atropine for relief but discovered that atropine made him worse. Years before he had been allergic to atropine. One tablet would "make him swell up and put him in bed for a week." On the basis of skin tests he was directed to avoid chocolate, tomato, Irish potato, eggplant, banana, grapefruit, orange, beef and veal. Further study showed by trial that coffee and eggs also appeared to predispose to anginal attacks.

During the following months his attacks were less frequent and less severe. They responded much better to the same dose of nitroglycerin. On one occasion he broke diet, taking coffee. This was followed by a severe attack which did not respond to the same dose of nitroglycerin. Sweet potato was later added to the list of the foods to be avoided. At the end of a month he began with rather more trouble. He had been taking theominal for a short time. Having discovered that this contained salicylates, he discontinued it, after which his angina was again relieved.

He then went two years, remaining on his diet and with practically no angina. He attributed this improvement to the diet. In February, 1936, he had "sinking spells" without much pain. Electrocardiogram showed evidence of coronary disease but no new thrombosis. He was retested with the foods, put on a new series of dietary avoidances. Early in July, 1938, he had a recurrence of angina, followed by coronary thrombosis. Two weeks after the thrombosis, he died.

Positive foods in 1936 were peas, beans, peanuts, grape, okra, parsley, celery, parsnips, carrots, rye, banana, beef, veal, walnut. Recurrence of symptoms may be attributable to changing sensitization. This patient was also positive to tobacco and had avoided it throughout the time.

He was a hypertensive subject, blood pressure having been as high as 240/110. On dietary restrictions it ranged around 140/95.

Shookhoff and Lieberman described a 63-year-old man with angina pectoris and at least one preceding attack of coronary thrombosis, in whom, during the ragweed season, anginal attacks became much exaggerated, occurring irrespective of exercise, food, etc. The attacks were relieved by ephedrine and later entirely relieved by the installation of a pollen filter. He was ragweed-positive, and formerly had suffered from ragweed hay fever.

Rowe reports a woman allergic to grass pollen, whose angina was greatly increased during the grass season and promptly relieved after installation of a pollen filter in her bedroom together with pollen hyposensitization.

Shookhoff and Lieberman have also reported 3 persons who developed angina following ingestion of acetylsalicylic acid. Two also reacted with urticaria. In 1, electrocardiographic changes occurred during the attack. Attacks repeatedly followed the taking of aspirin. In all 3 there was preexisting evidence of cardiovascular disease.

Green (1942) studied the skin reactions in patients with peripheral disease and those with coronary artery disease. He found that a much greater per cent of those with Buerger's disease with negative allergic histories gave positive

tobacco reactions than did normal controls. He also reported 4.5 times as many patients with coronary artery disease reacting to tobacco as did the general population.

Arrhythmias.—Duke reports that in certain cases reactive to heat, effort and cold, he can produce attacks of angina, extreme tachycardia or cardiac arrhythmia (ventricular extrasystole) by the application of the specific physical excitant, that he can increase tolerance by repeated exposures, and can relieve the condition with adrenalin.

Kern has described a middle-aged woman with paroxysmal tachycardia which could be precipitated by certain foods. The majority of these foods failed to react by skin test but the etiologic association appears to have been definite.

Harkavy (1938) reported three patients with tachycardia in two and auricular fibrillation in one, all of whom had other manifestations of allergy, who reacted to foods and inhalants by intradermal tests and who were relieved of their symptoms by removal of the offending foods from their diets.

Cardiac asthma.—Swineford finds that the majority of cardiacs developing classical cardiac asthma are allergic. The present writer has seen two cardiacs develop, not bronchial asthma, but typical acute pulmonary edema following exposure to extrinsic excitants. The excitants were orris root by inhalation and egg by ingestion.

Hypertension.—Although there is no constant or characteristic alteration of the blood pressure in clinical allergy, the pressure in the intervals between the acute allergic episodes is said usually to be normal or subnormal. Vaughan observed in a series of allergic individuals with asthma, eczema, vasomotor rhinitis, and urticaria, whose symptoms were relieved following allergic therapy, that 20.5 per cent had systolic pressure below 110 mm. Hg; 59 per cent were between 110 and 145; and 20.5 per cent had pressures above 145. Among those not benefited 27 per cent were below 110, 8 per cent above 145, and the remainder or 65 per cent within the normal range (110 to 145). Duke found in his series of pollinosis cases that the systolic blood pressure was normal in 40 per cent, below normal in 43 per cent, and above 150 in 17 per cent. In 2 cases the systolic pressure was above 200 mm. Feinberg states, "The general tendency for blood pressure in allergic conditions is to be low."

Most of the discussions of blood pressure responses in allergy have dealt with findings in bronchial asthma. Alexander states, "At the height of an asthmatic seizure there is usually a fall in blood pressure. Between paroxysms the blood pressure tends to be below normal. It is the exception to find increased pressures." In a series of 50 cases Alexander found only three with high systolic values ranging from 150 to 170 mm. The average was 118 systolic, 74 diastolic. The average age was thirty-nine years. Sihle also describes a fall in blood pressure during the asthmatic attack. Rackemann states, "A low blood pressure is common in asthma." Walzer writes, "It is generally admitted by most authorities that the blood pressure in asthma is usually normal or subnormal in the free interval between the paroxysms. Hypertension, however, is not an uncommon accompaniment of bronchial asthma."

Others describe an increase in blood pressure during the asthmatic seizure. Cooke states, "Between the attacks the blood pressure, both systolic and diastolic, is frequently low. When the readings are made during a paroxysm the systolic pressure is usually elevated, and this is due to the extraordinary

effort at respiration." Feinberg writes, "During the asthmatic paroxysm as a rule the pressure rises and varies markedly with inspiration and expiration." Kahn has described four patients with hypertension associated with severe intractable asthma in whom the administration of adrenalin was followed not only by relief from the asthma but also by a fall in blood pressure. In one case the systolic pressure fell from 200 to 140 mm. following the administration of 25 minims of epinephrine in a single dose. In another with initial systolic pressure of 260 mm., 1 cc. of adrenalin was given every fifteen minutes for four doses and then every thirty minutes for an additional two doses. At the end of this time the asthma was considerably relieved, and the systolic pressure had fallen to 175 mm. Later it fell to 148 mm. In his third and fourth cases, systolic pressures of 170 and 190 mm. fell gradually after several days of adrenalin therapy to 138 and 150 mm., respectively. He did not describe diastolic response. Cooke found that when hypertension accompanied asthma, the diastolic readings were not correspondingly elevated. He also observed that epinephrine promptly reduces the blood pressure.

These observations would indicate that hypertension is sometimes an accompaniment of the asthmatic paroxysm. The evidence does not enable one to determine whether the pressor response is a part of the allergic picture itself or whether it is, as suggested by Cooke, merely the result of respiratory effort.

Very little indeed has been written concerning the incidence of allergy in persons with essential hypertension. Kerppola found 5 per cent of 200 cases of essential hypertension to be asthmatics. Twelve of his series experienced an increase in pressure of from 25 to 100 mm. Hg during the asthmatic attack. At these times adrenalin administration was followed by a rapid return to the lower pressures.

Waldbott studied a young woman, aged thirty years, of a family many of whom suffered from hypertension and allergy. This woman four years previously had had a systolic pressure of 185 mm. At the time of Waldbott's first examination the blood pressure was 212 systolic, 115 diastolic. She was found allergic to milk, peas, beans, salmon, rice, and chocolate. Following the elimination of these articles from her diet, the pressure gradually fell to 145/92, and the allergic symptoms subsided. During the succeeding two years in which she followed her allergic restrictions, the systolic pressure ranged from 145 to 152 mm., the diastolic remaining around 90. At the end of this time the pressure again rose to 195/118. It was found that she had developed new sensitizations, to rabbit hair, horse dander, camel hair, glue, and coffee. In her occupation she was exposed to most of these substances. She was unable to change her occupation but remained strictly on her diet, avoiding the other allergens so far as possible. During the succeeding six months the systolic pressure usually ranged below 150 mm. By the end of this time the diastolic had gradually risen to where it usually stood around 107 mm.

These few reports indicate that hypertension may occur in allergic persons and vice versa; that in acute allergic episodes at least, adrenalin may cause diminution of the increased pressure; and that in allergic cases with essential hypertension, prolonged avoidance of the allergic excitants, especially foods, may be accompanied by a prolonged remission in the hypertension.

Vaughan and Sullivan (1937) described a middle-aged man with essential hypertension who was allergic to a number of foods. The eating of these foods caused pressor responses. On allergic dietary restrictions pressor episodes

above 155-160 systolic were eliminated to a great extent. Those few which were observed (up to 190 mm.) were easily traced to psychic upsets or to a break from the nonallergenic diet. The study covered a period of several months. The authors then studied serially the blood pressure response to ingestion of known allergenic and known nonallergenic foods in a series of 81 allergies. In only 2 was pressor response observed which could be considered beyond the normal range of fluctuation. In both instances the food was allergenic for the individual and other nonallergenic foods given to the same person caused no similar pressor response. The authors reached the following conclusions.

Discussion.—The three most characteristic responses both in experimental anaphylaxis and clinical allergy are (1) smooth muscle spasm, (2) serous exudation associated with increased capillary permeability, and (3) eosinophilia.

In view of the widespread distribution of smooth muscle in the vasculature, one would be justified in anticipating a pressor response in the allergic reaction. On the contrary, anaphylactic shock, both clinical and experimental, is characterized by a pronounced fall in blood pressure. Shock is, however, an extreme manifestation. The fall in pressure appears to be due to loss of fluid from the vessels consequent on increased capillary permeability. It is

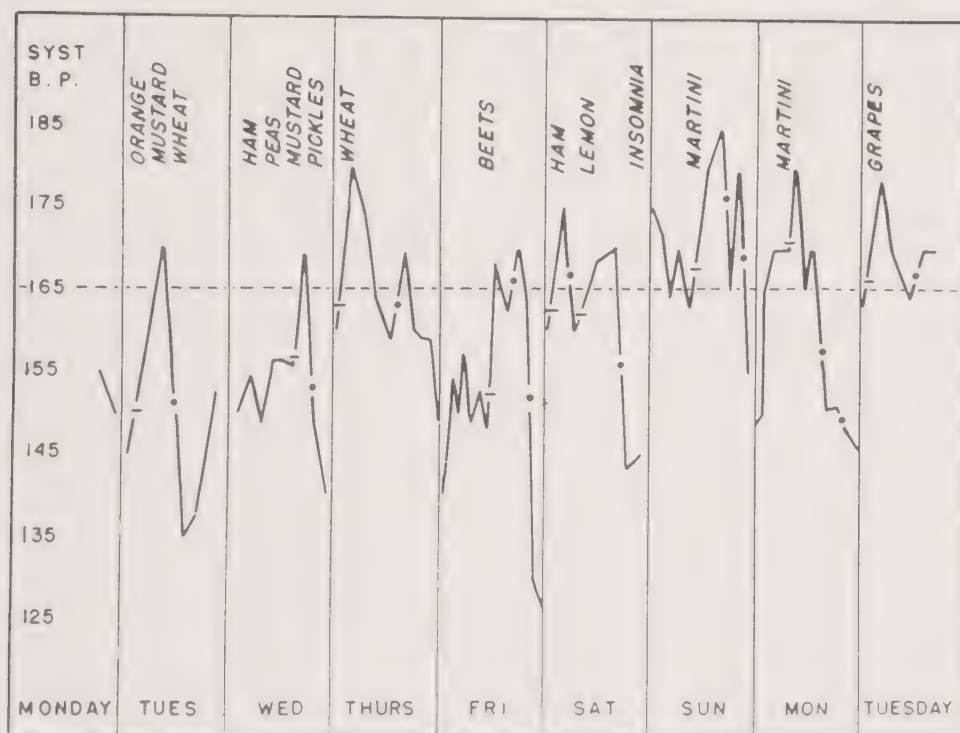


FIG. 330. Systolic pressure during eight days of observation prior to allergic restrictions. Foods listed above were those eaten prior to pressor episodes, and to which the patient was found allergic.

of especial interest in connection with the present discussion that in experimental anaphylactic shock in the rabbit and cat at least, there is a temporary rise in blood pressure, followed by fall. It seems logical to interpret this as being due, first to smooth muscle contraction in the smaller vessels, which is

later counteracted by loss of fluid due to capillary hyperpermeability. In a severe reaction the pressor response is masked by the phenomena of shock. In the absence of shock, the hypertensive response should be more clearly demarcated.

If this be true, the question will be raised as to why a hypertensive response does not occur regularly in allergy.

Waldbott and Ascher found that in human allergic shock there is an initial rise in blood pressure followed by a drop to below normal. There was an associated leukopenia, the intensity depending upon the severity of the reaction. Blood sugar curves showed an initial hyperglycemia followed by marked hypoglycemia. The eosinophile cells showed no characteristic changes. The pulse was slowed.

Doerr, likewise Coca, has presented the theory of the shock organ or shock tissue in allergy. Certain tissues of the body may be locally responsive in the allergic reaction. The commonest of these are the skin, the nasal mucosa, the

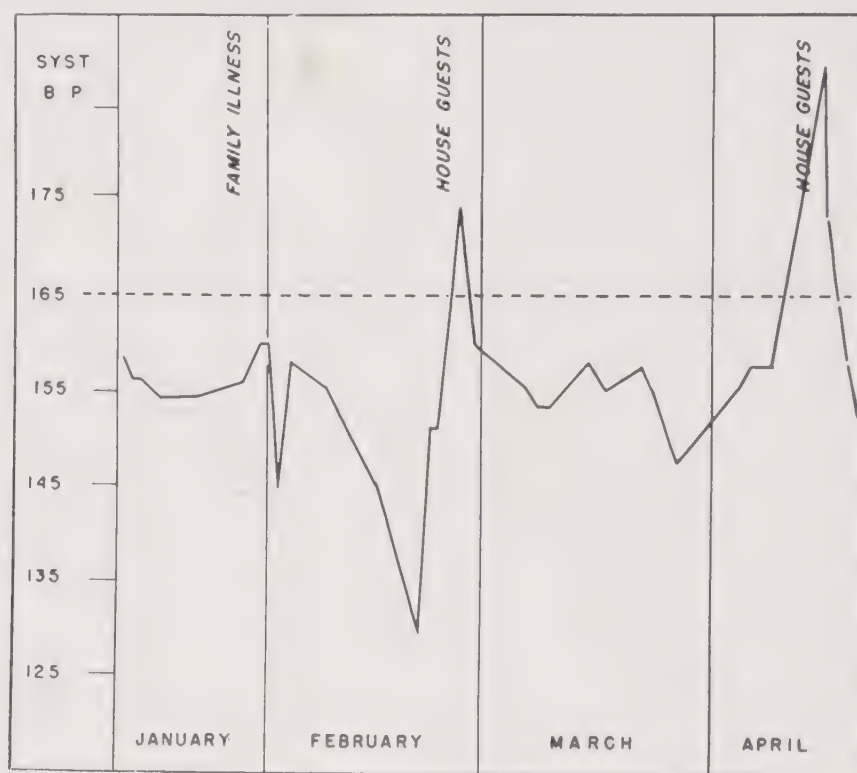


Fig. 331.—Blood pressure determinations for approximately four months after the imposition of allergic dietary restrictions (see Fig. 330). The general range of systolic pressure was lowered, peaks occurring only with disturbances of the customary routine. On the final peak in April the patient also temporarily discontinued his allergic dietary restrictions.

bronchi, and the intestinal tract. Experimentally the uterine musculature is also a shock tissue, as is demonstrated in the Dale phenomenon. There is evidence that either as a result of local tissue sensitization or some other as yet incompletely understood process, at times only one shock tissue may be responsive. Thus the hay fever patient reacts only in the nose. Sometimes two or more shock tissues respond simultaneously. The most highly responsive shock tissue in the guinea pig is that of the bronchial musculature while that of the rabbit is that of the vasculature of the pulmonary circulation. In the dog the most highly responsive shock tissue appears to be that of the portal circulation

There is evidence that the blood vessels of the kidney may respond to allergic excitants, with spasm.

In the absence of local sensitization in the shock organ, or of tendency to local response, one would anticipate no local response. The experimental evidence cited above suggests that smooth muscle of the vascular system may at times be an allergic shock tissue. Only in those cases in which the vascular musculature is locally sensitized or is an allergic shock organ might one anticipate the finding of allergic hypertension. Our observations would indicate that this occurs in a small proportion of allergic individuals.

Essential hypertension is a disease the etiology of which is, in last analysis, still unknown. The observations herein reported suggest that one contributory factor may be specific sensitization, provided the individual is allergic and, further, provided the vascular musculature happens to be a shock tissue in the individual case.

The existence of an allergic state would not be alone sufficient to produce essential hypertension. The hypertensive predisposition must also be present. In the presence of the latter, the former may determine pressor episodes. Whether this is through the mechanism of the vasculature as a shock tissue based upon a local chemical or colloid reaction or mediated through a reflex response can be determined only after more is learned of the mechanism of essential hypertension.

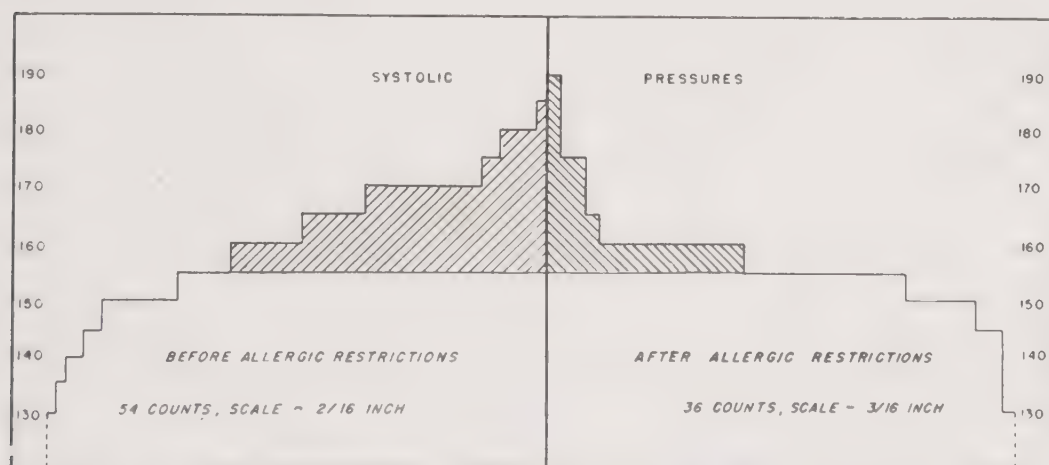


Fig. 332.—Comparison of pressor episodes before and after allergic treatment. The hypertensive responses were less frequent on allergic restrictions. The basic hypertensive tendency persisted, however, with most systolic counts ranging from 150 to 160. Allergy is not the basic cause of hypertension but may determine pressor episodes, thereby serving as an excitant.

The evidence would indicate that the avoidance of allergenic excitants, although diminishing the hypertensive response, does not eliminate the basic tendency nor does it bring the blood pressure back entirely to normal. This is also observed in Waldbott's patient in whom, although the systolic pressure fell from a high of 212 mm. to around 150 mm., where it remained fairly consistently for over two years, during this same interval the diastolic pressure which had fallen from 115 mm. to 92 mm. gradually climbed until after two years it was ranging around 107 mm. This would suggest a gradual progression of the basic pathologic process.

Liston (1937) reported 15 cases of allergic hypertension, 5 in detail. A woman with blood pressure ranging around 230/115 maintained a pressure around 140/80 as long as she avoided fresh pork. Other etiologic foods in

other cases included chicken, honey, milk, mustard greens, dandelion greens, wheat and chocolate. Pork was the most frequent offender in his series.

Gay describes relief from hypertension with allergic dietary restrictions. A woman aged 52, with blood pressure 205/105 eliminated allergenic foods. One month later the pressure was 155/75. At the end of the second month it was 125/70. During the following year the blood pressure was recorded at frequent intervals. It was never above 135/75. At the end of six years she discontinued her diet, eating all foods for a period of ten months. Her pressure was then found to be 210/105. Returning to a nonallergenic diet resulted in a fall of pressure within two weeks to 140/80. Later it fell to and remained around 130/70. The ingestion of wheat or milk in this case was regularly followed by extrasystoles or paroxysmal tachycardia. For the production of these symptoms, regular daily ingestion for three or four days was required. This was accompanied by a rise in systolic pressure of from 25 to 35 mm.

Gay also briefly mentions another case with hypertension, paroxysmal tachycardia and history of other allergic symptoms in which the tachycardia and hypertension have been relieved by dietary restrictions. He states that since 1934 he has treated 20 cases with essential hypertension in which there was no organic disease demonstrable and in all of whom there was definite history of allergy. The highest pressure recorded was 220/115, the lowest 150/80, average 180/90. Treatment consisted of allergic dietary avoidance only. Nineteen have maintained a blood pressure level of from 120/65 to 140/80.

Periarteritis nodosa. Gruber in 1925 discussed the findings in viscera diagnosed as periarteritis nodosa and suggested that the condition might be allergic. Kline and Young (1935) found tissue changes in the vessel walls in periarteritis which they considered characteristic of irreversible changes resulting from allergic inflammation. These consist of necrotic changes, edema, local eosinophilia, and smooth muscle hypertrophy. These were observed in the arteries of the voluntary muscles, the liver, gall bladder, coronary vessels, the lungs, and elsewhere. The following year Cohen, Kline, and Young made the diagnosis from biopsy tissue and stated that it was a severe allergic reaction in the vessel walls. Berger and Weitz and, the next year, Rackemann and Greene found asthma and periarteritis associated.

The condition is not so uncommon as was supposed. From the first description by Kussmaul and Maier in 1866 until 1939 only about 200 cases had been reported. To date the number is about 400. The difference in numbers is probably due to increased recognition of the condition. Arkin (1930) stated that the organs most frequently involved are the kidneys, heart, liver, muscles, peripheral nerves, and the gastrointestinal tract. Vessels of the skin, brain, or testicle may be involved.

There is a patchy scattering of the affected vessels, and various stages of the involvement may be seen at the same time. All coats of the vessels are involved. First there is a hyaline degeneration of the media followed by polynuclear infiltration with eosinophiles, lymphocytes, and plasma cells. Later there is proliferation of fibroblasts with partial or complete occlusion of the vessel. In the healing stage the lumen of the vessel may be reduced or completely obliterated and the wall replaced by fibrosis. Infarction and fibrosis are found in the affected organs, and aneurysms of the vessels are common.

The onset may be with chills and high fever, leucocytosis, possibly an eosinophilia, and manifestations of severe infection. The symptoms vary with the location of the process. They may be chiefly renal, cardiac, or neural. There may be icterus, splenomegaly, and adenopathy. Abdominal pain may be severe. There may be polyneuritis or polymyositis. The symptomatology is so varied that the diagnosis is confirmed only by biopsy or at autopsy, but many cases are now being diagnosed antemortem.

Rich (1942) found lesions characteristic of periarteritis in seven patients who had serum sickness and four of whom had also had sulfonamides, and, soon after, he published a report upon a typical periarteritis developing in a patient who was given sulfonamide. Rich and Gregory then showed experimentally that periarteritis nodosa could be produced in rabbits by establishing a condition analogous to serum sickness in man. They believe that periarteritis nodosa is a manifestation of the anaphylactic type of sensitivity.

Reiman (1943) reported two cases regarded clinically as trichinosis who developed lesions typical of periarteritis nodosa, and he suggested that trichinosis as a "disease with strong allergic manifestations may in certain instances serve as one cause of the syndrome called periarteritis nodosa." McCall and Pennoek (1943), however, reported ten patients with widespread necrotizing arteritis who had had neither serum nor sulfonamide and they considered the reaction to be a specific one but in blood vessels previously sensitized by some nonspecific toxin.

The present consensus is that this condition is an expression of sensitivity and is due to an antigen-antibody mechanism.

CHAPTER LXXVIII .

MISCELLANEOUS DISEASES

Loeffler's Syndrome. Loeffler in 1932 described this syndrome. He considered the condition a transitory and migrating pulmonary consolidation with high eosinophile counts, with almost complete absence of symptoms and physical signs. Fever rarely was present, and the patient's condition was good. The areas of consolidation moved from one area to another within a period of a few hours or a day or two. A positive diagnosis was made only by x-ray.

Various etiologic factors have been suggested. Engel (1936) reported patients who had seasonal recurrences, usually toward the end of May, while subsequent reports indicate an increased frequency of the condition in the mid-summer months. Meyer reported a patient with rhinitis, conjunctivitis, angio-neurotic edema, eosinophilia, with pulmonary consolidations. The condition apparently was due to pollen. Hansson found two children infested with ascaris and with pulmonary consolidation. Wright and Gold found in 26 cases of creeping eruption that there were nine who showed pulmonary infiltration, blood and sputum eosinophilia, and few other signs or symptoms. Skin tests with worm extract gave positive reactions in 23 of the 26. Randall reported a patient whose symptoms and signs cleared under ten daily injections of emetine and he thought the condition might be due to amoebic infection. Miller's case had 85 per cent eosinophilia without any etiologic factor which could be discovered. Treatment with Mapharsen was successful.

Symptoms are few, and none is characteristic of the condition.

Blood changes are limited to the eosinophilia which may be quite marked.

The diagnosis is usually made by x-ray findings which show a pulmonary infiltration which moves about and which, on this basis, may be differentiated from other pulmonary lesions. Hennell and Sussman gave a very satisfactory description of the lung findings and reported five patients, two of whom died. These two were believed to have had periarteritis nodosa. Biopsy done on one showed typical necrotizing lesions of the vessels.

Many reports have appeared in the past few years probably indicating recognition of the condition rather than its rapid increase. Harkavy (1941) reported eight cases with pulmonary infiltration, asthma, polyserositis, and with eosinophiles in the sputum, the serous exudates, and in the perivascular infiltrations in the skin. He did not believe these were true Loeffler's disease because of the prolonged pulmonary infiltration and the large effusions.

The pulmonary infiltration is believed to be due to transient focal edema (Pierce). Bayley reported the finding at autopsy of numerous irregularly shaped areas of increased density which were grayish yellow, firm, and resembled tubercles. In the lower lobes they were larger, dark red, and softer. There was considerable serosanguineous fluid in the pleural cavities, and the bronchi contained much mucosanguineous exudate. Sections from the consolidated areas showed masses of fibroblasts and collagenous fibers with many eosinophiles, plasma cells, lymphocytes, and a few giant cells. Some areas contained acid-staining granular necrotic material with multinucleated cells and fibroblasts between the clumps of necrotic debris. Eosinophilic granules and large his-

tiocytes, epithelioid cells, and fibroblasts were surrounding the central area of the lesion. In the outer zone were eosinophiles, plasma cells, and lymphocytes. These lesions had the appearance of the lesions of rheumatic fever rather than tuberculosis. There was a marked inflammatory process in the arterial walls with areas of necrosis. No bacteria were found.

Except in those patients in whom a definite etiologic agent can be implicated, treatment must be symptomatic. Arsenic has been reported to be of value.

The prognosis is good. It is probable that many of these cases are undiagnosed. Among those that are, the mortality rate is low.

Tropical eosinophilia.—This condition has been described only recently. The first cases reported were found in north India, and later from Australia and Singapore. With the return of men from military service in various parts of the world, it has been reported in European soldiers, and a few American cases have appeared.

The etiologic factor is not known. It is believed to be an allergic reaction. It may involve all ages, races, and classes of people. There is no seasonal variation, and the condition persists after removal of the patient from the area in which he contracted the disease.

The disease usually begins with a feeling of malaise, anorexia, weakness, and fever which is usually not high. A dry, hacking cough, usually nocturnal, develops, and a wheezing expiratory dyspnea ensues. There is a leucocytosis and rather high eosinophilia.

Examination reveals sibilant and sonorous râles and prolonged expiration. The sputum is scanty, tenacious, and glassy, with a considerable number of eosinophiles in it. In the acute stage about one-half of the patients have enlarged spleen. There is a mild degree of anemia with leucocytosis and high eosinophilia, and a moderate increase in the sedimentation rate. There are no significant changes in the blood chemistry. The urine and feces show nothing significant.

The radiologic findings of the lungs are increased bronchial markings (Hirst and McCann), a mottling which disappears after the first week (Hodes and Wood), or an appearance not unlike that of miliary tuberculosis (Emerson).

No autopsy reports have appeared.

There is some question as to the identity of this disease. It is difficult to distinguish from Loeffler's syndrome. The pulmonary infiltration and high eosinophilia may also be found in asthma and in periarteritis nodosa. Without added knowledge regarding the etiologic agent there will probably continue to be confusion in the differentiation.

Arsenic has been used in the treatment of this disease, and the response is so dramatic in many instances as to suggest a spirochetal etiology for the disease.

Epilepsy.—That epilepsy may be associated with allergy, particularly food allergy, is by no means a new suggestion. The conception probably had its earliest origin in a realization of the apparent similarity in many features between migraine and epilepsy. However, in spite of a number of articles tending to show that there may be an allergic factor in this disease, allergic treatment appears to have gained little headway. I have studied no large number of epileptics, allergically. I have seen a few cases, particularly in children, in whom specific dietary restrictions have appeared to be beneficial. I have

seen vastly more in whom we were able to establish nothing. Evidence to date precludes any great degree of enthusiasm for allergic idiopathic epilepsy, but it still remains possible that with improvement in methods of diagnostic study of the food allergies, future evidence will be more convincing.

As far back as 1904 Spratling suggested that food idiosyncrasy might be an etiologic factor in some cases. In 1919 Pagniez and Lieutaud noted leucopenia in an epileptic patient following the ingestion of chocolate, a food which regularly caused convulsions. Ward (1922) suggested protein sensitization as a cause of epilepsy. Howell (1923) reported skin tests on 14 epileptic children, 13 of whom reacted to one or more foods. Wallis, Nicol and Craig (1923) tested 122 epileptics, finding 46 food-reactive. McCready and Ray (1924) reported 9 cases in which food allergy appeared to be a factor in the causation of convulsions. Ward and Patterson (1927) observed positive skin reactions in 37 per cent of 500 patients at the Craig Colony for Epileptics and 56.8 per cent of 500 patients at the New Jersey State Village for epileptics. Among 100 controls only 8 per cent gave positive reactions.

Spangler (1927) stated that food histories or food diaries were more valuable in the study of allergy in epilepsy than the usual method of skin testing.

Adamson and Sellers (1933) found that the occurrence of allergic manifestations in the antecedents of epileptics is higher than in normal individuals, but lower than in persons with hay fever and asthma. They found a low incidence of hay fever, asthma and eczema in epileptics. They found atopic reagins in 11 per cent of 100 epileptics. This was a much lower incidence than in other allergic conditions such as hay fever and asthma.

We may conclude with regard to epilepsy that there is conflicting evidence; that in familial allergy epilepsy has not been proved to fit definitely into any of the interlocking facets displayed by the other allergic diseases; that while there may be an allergic factor in epilepsy and evidence such as that just described is suggestive, until someone presents more convincing proof, in the nature of relief in a large series following allergic methods of therapy, idiopathic epilepsy must be cataloged as a primarily nonallergic disease in which occasionally allergy, particularly food allergy, may serve as an exciting secondary factor.

Wilmer and Miller report a case of epilepsy relieved following the application of Rowe's elimination diet in spite of failure of relief following specific dietary restrictions based upon positive skin reactions. Forman describes 10 cases, relieved by allergic dietary restrictions. Three were still symptom free at the end of nine years.

There is much clinical evidence that sensitization may be local in certain tissues of the body. This would explain the observation that a single individual may experience migraine from eating Irish potato, colitis from carrots and urticaria from celery. Davidoff and Kopeloff did craniotomies on 35 dogs and applied horse serum, egg albumin and other allergens directly to the brain, through the wound. No symptoms followed this primary application. Intravenous injection of the sensitizing substance after several days resulted in weakness on the opposite side of the body from that into which the preliminary substance had been introduced in the brain. They interpreted this as evidence of localized cerebral sensitization in the region of the motor areas.

Ménière's disease.—Duke, Rowe, and Richet all described this condition as allergic, and a few reports have appeared in later years. Williams (1947) believes that true Ménière's syndrome is an allergic condition. Autopsy findings

in authenticated cases are "gross dilatation of the endolymphatic system chiefly of the scala media and the saccule and utricle. Degenerative changes are found in the organ of Corti and at times in the stria vascularis. Inflammatory changes have been conspicuously absent." He believes this is not an antigen-antibody mechanism but due to physical allergy. Treatment consists of restriction of fluid, reduction of salt intake, enteric coated tablets of potassium nitrate (1 to 2 Gm.) with meals, and nicotinic acid hypodermically beginning with 25 mg. and increasing by this amount until usually a dose of 100 mg. is reached and held.

Other neurologic symptoms.—Peripheral neuritis is seen occasionally in serum sickness. It has been described as a symptom of allergy to foods and other excitants (Vaughan, McKay, Campbell and Allison). An allergic factor in trigeminal neuralgia has been mentioned by Rowe (1928), Brown (1934) and Vaughan (1930). My own experience leads me to believe that it is not the cause of the disease and that while it may be a factor in causing exacerbation of symptoms, trigeminal neuralgia is not relieved adequately by allergic treatment alone.

Personality changes have been described, particularly by Shannon who observed remarkable improvement in disposition and scholastic aptitude of children after the avoidance of allergenic foods. Persons who are otherwise allergic often find that when placed upon an appropriate diet their sensation of constant fatigue or of mental depression amounting almost to psychasthenia is remarkably relieved, to return following breaks in the diet.

Allergics, especially allergic children, are fidgety. The children find it difficult to stay still, and during the diagnostic study they are usually wandering about, asking all manner of questions. Sometimes the condition is so marked as to suggest mild chorea. Duke has pointed out that the allergic parent of an allergic child is apt to be similarly fidgety and unnecessarily anxious and attentive during the child's examination.

Genitourinary symptoms.—These are infrequent. They include frequent and painful urination, tenesmus, urinary retention (due to urethral edema), renal colic, enuresis, vulval irritation and balanitis which may be due to the action of absorbed allergen or allergen locally applied as medication or contraceptive.

Enuresis may be associated with allergy, more particularly food allergy. It may be the only allergic manifestation or may accompany other symptoms of allergy. Bray reported the allergic study of 15 children with enuresis. Three were relieved following the avoidance of positive foods.

Menstrual disturbances have been reported as dysmenorrhea and menstrual irregularity.

Arthritis.—The factor of bacterial allergy in arthritis and the arthritic response in serum sickness have been discussed. Harkavy and Hebal report a small series of asthmatics with associated arthritis. They found no evidence of atopic sensitization and ascribe the etiology to bacterial allergy. Young found no correlation between chronic arthritis and food allergy. There was a high percentage of skin allergy (past or present) in arthritic patients, but the reverse did not hold. A group suffering primarily from skin allergy did not have a high incidence of arthritis.



Fig. 333.—The nervous or psychic factor in allergic responses. This patient's abdomen would balloon up, as shown above, within three minutes after eating certain foods, especially orange juice, or after dipping the hand in ice water. Photograph was taken with the latter as the excitant. Breath holding or other obvious diaphragmatic manipulation did not accompany this response. The back is not arched. The ballooning persisted although the patient continued to breathe normally. Relief followed dipping the hand in hot water. Abdominal distention is a frequent feature of gastro-intestinal allergy. However in the above case the extreme degree and rapidity of response suggests a predominant psychic factor. The patient was not of the hysterical type. Allergic food avoidances have given relief through the two intervening years. Allergic therapy relieved, possibly through suggestion.

Rich and Gregory found that a large per cent of rabbits with experimental serum sickness showed cardiac lesions resembling rheumatic carditis. They also state that focal injury to connective tissue is common in both conditions; rheumatic arteritis resembling periarteritis nodosa occurs in rheumatic fever; skin manifestations of serum sickness type occur fairly frequently in rheumatic fever; purpura is common to both; tissue eosinophilia may be found in the rheumatic heart; acute rheumatic fever, like serum sickness, has fever, arthritis, anaphylactic, cutaneous and arterial lesions, and the synovial exudate from the arthritis of serum sickness is identical with that from rheumatic joints. They also found the lesions of rheumatic pneumonitis identical with the pneumonitis due to sulfonamide sensitivity.

Intermittent hydrarthrosis.—The only form of arthritis in which there has been any large amount of evidence of an atopic factor, especially food allergy, has been intermittent hydrarthrosis. Such patients should be studied allergically but the possible bacterial factor should not be neglected.

Miller and Lewin (1924) first suggested a sensitization factor in intermittent hydrarthrosis. A recent report by Lewin and Taub (1936) is of special interest in illustrating the possible delayed character of the reaction. Attacks had been intermittent for ten years. Skin reaction was positive to English walnut and its ingestion was followed in 72 hours by a typical attack. Autopassive transfer was done, the patient's serum being introduced into his own skin. He then ate liberal quantities of walnut. Within two hours the transfer site was positive, control negative, but he did not notice swelling of the joints until three days later. Thereafter the condition persisted for five or six days. Assuming that such a case might present a false negative skin reaction, the difficulty of tracing the excitant by means of the food diary becomes apparent. The interval between ingestion and reaction is confusingly long.

Gout.—A number of workers have suggested an allergic background for gout, since the first communication of Billard (1910). Among the more extensive analyses are those by Chauffard (1922), Widai, Abrami and Joltrain (1925), Llewellyn (1927), Gudzent (1935), and Vallery-Radot (1937). It will be recalled that as early as 1850 Trousseau included gout with urticaria, asthma, migraine, etc., in the exudative diathesis. Recent European contributions still emphasize the alternation of gout, asthma, urticaria, acute circumscribed edema and migraine. Vallery-Radot points out that when gout is due to alcoholic beverages, only certain specific ones will cause the gouty reaction. It is not a matter of all wines causing the disease, but of one or a few types of wine doing it consistently while others may be taken with impunity. Those who ascribe an allergic background consider the uric acid deposits in the tissues as of secondary importance, the tissue response being primary. The latter has been described as a hyperergic inflammation with fibrinoid necrosis. Diaz (1932) believes that gout is basically an allergic disease and that a defect in uric acid metabolism exists in all allergies.

Leri wrote "The acute attack of gout presents obvious similarities to the anaphylactic reaction: the suddenness of the attack which begins just a few hours after the absorption of a minimal quantity of a certain food, often identical for one invalid but different for others; after the absorption of a glass of champagne or the eating of a truffle; the violence of the attacks and their intense congestive character; the nervous and digestive symptoms which often accompany them; their sudden disappearance, are all characteristics which are common to gout and to the phenomena of anaphylaxis."

Llewellyn points out that sufferers from gout are extremely sensitive to a number of foods many of which are not at all rich in purine and some of which such as beer and wine contain none at all. He points out that the diet for gout gives relief when foods that are frequently allergenic are avoided, with no consideration of their purine content. He believes that gouty persons are sensitized to certain specific proteins. In beer he suspects the hordein of malt and the gliadin of other cereals. In wine he suggests the possibility of sensitization to yeast. In gout due to lead he suggests a hapten action, the lead combining with body protein to form a foreign protein.

Vallery-Radot after a comprehensive review of the literature concludes that although the allergic origin of gout is not proven the preponderance of evidence favors such an explanation.

Otologic symptoms.—The only two symptoms so far reported of significance are catarrhal deafness, usually associated with allergic coryza, and dermatitis of the external ear which may be atopic (foods) or contact (feathers, dust, earphone, hair dyes, cosmetics, etc.).

Ocular allergy. Considerable experimental and clinical investigation has been done on ocular allergy. The work up to 1933 was reviewed by Wood while additional work to 1936 has been summarized by Hansel. The wide variety of clinical allergic ophthalmic disturbances is illustrated in the recent discussion by Ruedemann.

This author has observed a surprisingly high incidence of allergy or, better, of an allergic factor in certain ocular diseases. He remarks that a number of lesions, particularly those of the fundus, have characteristics of both allergy and infection. Both etiologic factors may coexist as in nasal allergy.

Conjunctivitis and *blepharitis* may be allergic, with perennial or seasonal symptoms. Seventy-eight per cent of 139 cases of conjunctivitis and blepharitis had clinical disorders of an allergic nature. Allergic conditions of the upper respiratory tract predominated. Elimination of offending allergens sufficed in the majority, but in from 30 to 35 per cent hyposensitization was also required.

The following are illustrative cases. A druggist with severe *conjunctivitis* was found allergic, not to certain drugs as one might anticipate, but to feathers and house dust. Avoidance relieved his conjunctivitis. A boy with severe conjunctivitis was found allergic to chocolate, milk, banana, orange, carrot, celery. Relief followed dietary restrictions.

A patient with *vernal catarrh* and history of recurring *keratoconjunctivitis*, *corneal ulceration*, *chalazion* and *blepharitis marginalis ulcerosa*, was relieved after avoidance of allergenic foods and inhalants and desensitization with extracts of pollens, molds and house dust.

Even when the cornea was involved along with the conjunctiva in *keratoconjunctivitis*, allergy was found at times to play a part. Sometimes the attacks of recurrent corneal involvement had even progressed to scarring. In these cases the chief offending allergens were pollens, house dust, molds, orris root, epidermals and, occasionally, foods. In this condition as in the other manifestations of ocular allergy, treatment consisted of the customary local therapy such as holocian and epinephrine ointment, 3 per cent ammoniated mercury ointment, ocular rest, dark glasses, etc.

In this last series contact allergy was found to be the most frequent factor, followed by inhalant and ingestant allergy. Orris root is mentioned as 33.

important factor in some cases. Local treatment for the acute exacerbation combined with allergic therapy as a preventive produced satisfactory relief in 80 per cent. Recurrences invariably followed failure to adhere to the allergy regimen.

A woman had severe superficial *keratitis*, severe *conjunctivitis*, recurring *chalazion* and *ulcerations of the lid*. Permanent relief followed dietary regulations together with coseasonal pollen desensitization. Another patient with similar complaint in whom the local pathology had progressed to the stage of denudation of the cornea was partially relieved following desensitization with house dust and tuberculin. Following a recrudescence pollen sensitization was recognized. Tuberculin therapy was discontinued. Hyposensitization against dust and pollen was inaugurated, with excellent relief through the next pollen season.

Ruedemann describes external ocular allergy associated with allergy to contact substances such as butyn, relieved by avoidance. These lesions may progress to corneal ulceration.

Seasonal conjunctivitis or "vernal catarrh" is usually due to pollen, and treatment on that basis is usually satisfactory. Bowen (1941) called attention to the fact that these cases are probably contact reactions and that treatment with pollen oil or oil together with water-soluble fractions of pollen gave best results. Some instances of this type of conjunctivitis are due to molds but these are usually not definitely seasonal.

Nonseasonal conjunctivitis may be due to medication used in the eye and may be associated with a contact dermatitis of the lids. It should be remembered that sometimes a drug which is being used for relief of conjunctivitis from another cause may perpetuate the condition. A physician who had a vernal conjunctivitis from an early blooming weed used Butyn in the conjunctival sac for relief from the irritation. Instead of clearing, as it usually did, with the end of the pollen season, the conjunctivitis continued until it was found that the drug which gave him temporary relief from the discomfort was actually the cause of it.

Cosmetics, nail lacquer, and other substances producing a contact dermatitis of the lids, seldom involve the conjunctiva.

Noninflammatory *edema of the optic discs* and noninflammatory *chorioretinitis* may be based upon an allergic factor. Angioneurotic edema and migraine are frequent accompaniments in this group. Food allergy appears to be the commonest allergic factor. Allergy to tuberculin was observed in from 30 to 40 per cent. The author stresses the importance of general care and the correction of any residual foci of infection. In view of the latter he makes no attempt to evaluate the influence of allergy in lesions of the fundus in the series studied. He states, "We know that allergy is a factor in such cases, and we believe that the edema of allergy is a contributing factor in prolonging recovery. . . . Observation of a larger series of patients over a longer period of time will be helpful in arriving at a definite conclusion regarding its importance."

The author emphasizes that the cases include those in which no evidence of focal infection or other apparent etiology could be established, cases in which such studies had been carefully carried out before considering allergy as an etiologic possibility. "To anyone practicing ophthalmology, it is apparent that the cases presented are those heretofore unexplained for the most part. We have found that many patients have had all foci removed and the

problem has been to find some cause for the recurring symptoms. We are aware that allergy is not the cause of all eye conditions, but we have had sufficient evidence to warrant further investigation and to continue this form of treatment which has produced both symptomatic and physical improvement."

Table LXXXI by Ruedemann illustrates the frequency with which persons with ocular pathology manifest other common allergic symptoms.

TABLE LXXXI. OPHTHALMOLOGIC ALLERGY
514 CASES OF CLINICAL ALLERGY

CLINICAL DIAGNOSIS	NUMBER OF CASES	PERCENTAGE
Perennial allergic rhinitis and bronchitis	137	26.9
Bronchial asthma	113	22.1
Pollinosis (seasonal hay fever and asthma)	76	14.9
Ocular allergy	51	10.0
Allergic eczema	37	7.2
Allergic headache	29	5.7
Urticaria	27	5.2
Gastrointestinal allergy	25	4.9
Food allergy	10	1.9
Genitourinary allergy	5	0.9
Salivary glands	4	0.8

CONJUNCTIVAL AND LID MANIFESTATIONS OF ALLERGY

External dermatitis	5 cases
Conjunctivitis	131 cases
Blepharitis marginalis sicca	2 cases
Blepharitis marginalis ulcerosa	2 cases
Meibomianitis (chronic)	4 cases
Chalazion	3 cases
Total number of cases	147 cases

PRESENCE OF ALLERGIC STATES IN CONJUNCTIVITIS AND BLEPHARITIS

Total number of cases	139
Cases with clinical manifestations of allergy	108
Diagnoses of allergy:	
Allergic rhinitis	59
Gastrointestinal allergy	29
Allergic dermatitis	11
Migraine	6
Allergic headache	5
Bronchial asthma	3
Total diagnoses of allergy	113

EXTERNAL DERMATITIS

Total cases of external dermatitis	5
Cases with clinical manifestations of allergy	4
Diagnoses of allergy:	
Gastrointestinal allergy	2
Allergic rhinitis	2
Allergic dermatitis	2
Total diagnoses of allergy	6

ASSOCIATION OF KERATOCONJUNCTIVITIS AND ALLERGY

Total cases of keratoconjunctivitis	42
Cases with clinical manifestations of allergy	22
Diagnoses of allergy:	
Allergic dermatitis	4
Allergic rhinitis	14
Bronchial asthma	1
Gastrointestinal allergy	5
Total diagnoses of allergy	24

TABLE LXXXI—CONT'D

ASSOCIATION OF NONINFLAMMATORY EDEMA OF DISCS WITH ALLERGY

Total number of cases		14
Clinical manifestations of allergy		13
Diagnoses of allergy:		
Gastrointestinal allergy	7	
Allergic rhinitis	5	
Migraine	2	
Allergic headache	2	
Total diagnoses of allergy		16

LESIONS OF THE FUNDUS

Edema of disc (noninflammatory)	14	
Chorioretinitis	17	
Neuroretinitis	7	
Optic neuritis with optic atrophy	2	
Total number of cases		40

CHORIORETINITIS

Total cases of chorioretinitis		17
Total cases with clinical manifestations of allergy		9
Diagnoses of allergy:		
Migraine	1	
Gastro-intestinal allergy	4	
Allergic rhinitis	5	
Total diagnoses of allergy		10

Conclusions

It should be borne in mind that many of the diseases discussed in the preceding pages are not primarily allergic. Allergy is but one among the possibilities. Other usually more important diagnostic and therapeutic considerations should receive due attention. On the other hand, even though other causes have been established, it is possible, especially if appropriate treatment has not given anticipated improvement, that allergic methods may aid materially.

The number and variety of allergic manifestations herein described are so great that it would not be surprising to find further additions to the list in the future. However, the original allergic diseases, hay fever, asthma, urticaria, acute circumscribed edema, dermatitis, migraine and gastrointestinal allergy, account for by far the majority of cases. The writer does not anticipate many additions to the list. Many of the unusual symptoms mentioned are so infrequently allergic that the literature contains little more than individual case reports. Since allergists have without doubt been watching for similar allergic responses in primarily nonallergic diseases and yet have added no great number of case reports to the literature, we may safely presume that instances will remain infrequent. At the same time this does not justify one in ignoring the allergic possibilities in primarily nonallergic disease when such a possibility has been shown to exist. For the proper utilization of all of its helpful potentialities, the practice of allergy cannot be divorced from the practice of internal medicine.

CHAPTER LXXIX

THE NEED FOR CONTINUOUS LIFE-RECORDS

In the final analysis, the student of allergy is in great measure a student of life. The study of allergy is the study of the reaction of living cells to their environment and to alterations in the environment. In observing altered reactions of living cells to those substances, living or dead, which surround them, we may hope some day to learn more of the normal life responses. The allergist must treat disease but he should realize that the disease under investigation is but an end result, a tangible manifestation of a deeper, more fundamental biochemical reaction, the mysteries of which must be solved before a complete understanding of allergy is arrived at.

It is only while the reactive subject is alive that responses occur which may be adequately studied. The allergist gains relatively little information from the autopsy protocol.

It is not surprising therefore that in the predisposed, reactions of an allergic character may appear in the earlier ages, even at birth. Indeed, the predisposing background may be followed still farther back, in the allergic inheritance of preceding generations.

The concept that, for a better understanding of disease it must be studied in its incipiency, or better even before it commences, so that susceptible terrains may be recognized, is in no sense new. Leading clinicians have written essays on the subject. A few years ago the periodic health examination was proposed as a measure toward this goal. Sir James MacKenzie when 65 years old, gave up a splendid consultative practice in London to establish a small clinic at St. Andrews, Scotland, so that he might learn something of the earliest manifestations of disease. He realized that clinical material in the great metropolitan hospitals was limited in great measure to the late results of disease-invasion and that such cases would never provide adequate opportunity for the study of predisposing influences and earliest manifestations. He selected a small town with a stationary, nonmigrating population which also had a good medical school. Here he hoped, through a long-time study of persons sick and well, to discover more concerning the origins of disease.

The objectives of the St. Andrews Clinic were outlined as follows: "The main objects of research would be the early stages of disease, and the work would primarily consist of detailed observations of symptoms and the keeping of careful records. Prolonged observation of cases would be carried out in order to discover the significance of early symptoms, and researches would be undertaken with a view to ascertaining the mechanism of their production." We may hope that since the death of this great physician these objectives will still be strived for in this same clinic, now The James MacKenzie Institute for Clinical Research.

A similar long-time survey has been inaugurated in Cleveland under the able direction of the late T. Wingate Todd, in "the longitudinal study" of children, by the Associated Foundations. In this study much attention is given to the earliest appearance of allergic manifestations.

Allergy provides the best series of basic phenomena for the formulation of a continuation-record of the life-and-disease history of a person from birth to death. Its seed is planted with the fertilization of the ovum. It may crop up at any time during life, from the earliest years. It may recur intermittently throughout life. It may modify the picture of other disease. It may modify the life of subsequent generations. In the individual, it terminates with death. A life history which records only the acute illnesses of childhood and the degenerative diseases of advancing years, will be but a record of the morbid episodes of the subject, and notations will be decidedly intermittent. A record of one's allergic experiences would be likely to contain notations for every year of life and would in great measure be actually the life-record of the individual. When we realize the high percentage of the population affected by allergy, major and minor, we must grant that such a life record could be used with practically all persons and that in the entire series there would be no more than enough negative controls.

This idea, even as it applies to allergy, is not new. As early as 1885 Jonathan Hutchinson, in discussing idiosyncrasy, diathesis and kindred conditions, stressed the desirability of "life-records." A person's medical history should commence at birth and be kept throughout life until death. It should be available, "to be produced to any medical man who may be consulted" and should especially comprise mention of family tendencies, individual idiosyncrasies and the diseases which have been passed through.

"There are few of us without our idiosyncrasies and the variety is innumerable. If it should become the custom for parents to record some sort of life history of their children in permanent form from birth or infancy onward, noting all the peculiarities in an individual by the aid of medical observation, not only would much be done in the way of preventing subsequent errors in the treatment of disease but valuable contributions would be made to our knowledge of its real nature. It is not only as regards the prescription of our drugs that a knowledge of our patient's peculiarities becomes important for use in practice. The advice we have to give in respect to places of residence, mode of life, and of general management is often of far more importance than the medicine prescribed. Its wisdom or the reverse may depend on our knowledge or ignorance of the individual peculiarities, and those peculiarities frequently do not display themselves in any of the existing symptoms, but can be recognized and revealed only by a correctly kept life-history."

Today the newborn baby receives as his first gift a dainty little pink or blue book with some such happy title as "Baby's Life." In it one finds beautifully decorated pages for recording the date of baby's first laugh, first words, first shoes, first tooth, first short clothes, first steps, favorite toys, first Christmas, first prayer, favorite sayings and the like. While the value of these to posterity is questionable, there is usually also space for a very brief listing of the family tree and for records of growth in height and weight. Some of the more advanced books have spaces for records of childhood diseases and for smallpox vaccination and diphtheria inoculation.

This idea might well be enlarged upon to provide adequately for the medical history of the individual. In this day of high-grade nearly indestructible looseleaf binders and of equally high-grade heavy paper, a looseleaf indexed system would appear preferable. Each person would carry his book to his physician at intervals, possibly annually, for the insertion of notations. He himself would make frequent notations through the year, which would be

condensed and summarized for the permanent record. Especially important for inclusion would be records of abnormal reactions, food and drug idiosyncrasies, and the date and precise nature of various inoculations and the response thereto, serum injections being especially important.

One might object that, knowing so much about themselves, many of the owners of such books would become too introspective, hypochondriacal. The writer has observed that in the last twenty-odd years since men and women have been emancipated from the repressions of the Victorian Age and have adopted more natural psychologic and biologic attitudes, hysteria and neurasthenia have become much less pressing problems. The neurasthenic maiden aunt has given place to the self-controlled efficient unmarried business woman. In our allergic practice we have consistently avoided any semblance of secrecy or mystery as concerns the patient and have found that practically without exception, best results are obtained if he or she understands correctly the intricacies of the allergic problem and program.

If we are to derive maximum knowledge from such a life-record it should be supervised or edited from time to time by one especially trained in the procedure so that, later on, investigators with special interest in any group of the diseases to which flesh is heir, could acquire useful information therefrom.

Ramsay wrote quite truly, "We must look to the living to learn the laws of life, not to the dead."

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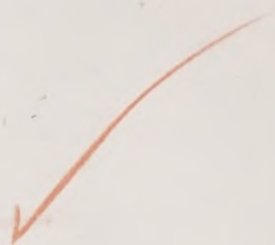
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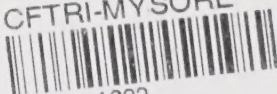


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